Exploration of [2+2+2] cyclotrimerisation reactions of alkynes

A new methodology for the synthesis of small molecules to probe biological systems

Ana Rita NEVES DOS SANTOS

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Institute of Cancer Therapeutics
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[2+2+2] cyclotrimerisation, alkyne, biological probe, Diversity-oriented synthesis (DOS), [2+2+2] cyclotrimerisation, tetrahydroisoquinoline, alkynes, transition-metal chemistry, organometallic chemistry, microwave chemistry, tetrahydronaphthyridine, dihydropyrrolopyridine.

The generation of new chemical entities (NCEs) for use in chemical biology and drug discovery is of wide interest to both academia and the pharmaceutical industry. In order to generate NCEs, this project focused on development of new synthetic methodologies using transition-metal mediated [2+2+2] cyclotrimerisation of alkynes and unsaturated molecules to form bi- and tricyclic heterocyclic derivatives, some with structural resemblance to the quinocarcin family of natural products. Three different dialkynes (1,5-di(prop-2-yn-1-yl)pyrrolidin-2-one **2.117a**, 1,6-di(prop-2-yn-1-yl)piperidin-2-one **2.118a** and 4-benzyl-1,6-di(prop-2-yn-1-yl)piperazin-2-one **2.120a**) were successfully synthesised. Several cyclotrimerisations were attempted, with the best yields being obtained when diethylacetylene dicarboxylate **2.113a** was used as the monoalkyne and Cp*Ru(cod)Cl as the catalyst in refluxing toluene. New heterocyclic compounds with potential for diversification were synthesised using a diversity-oriented synthesis approach; specifically the build/couple/pair strategy for the synthesis of small molecules. Racemic nitrogen and oxygen building blocks were coupled with acrylonitrile, bromoacetonitrile and acyl chlorides. The pair step involved the intramolecular ring closure using transition-metal catalysed [2+2+2] cyclotrimerisations using microwave assisted radiation. The best catalyst for this approach was found to be $CpCo(CO)_2$ at 150 ºC (300 W) in chlorobenzene. This provided a new methodology with potential for synthesising a diverse set of small molecules for biological testing. 20 compounds were subjected to chemosensitivity testing using the MTT assay. Several compounds were shown to possess activity in bladder (RT112) and breast (MCF-7) cancer cell lines. As these two cell lines are known to express extra-hepatic cytochromes P450 enzymes, it is possible that these are involved in generating cytotoxic metabolites that may damage DNA.

Damian W. Young, Ph.D.
7 Cambridge Center
Cambridge, MA 02142
T 617-714-7000 F 617-324-9601

April 22, 2013

University of Bradford

Bradford, UK

Re: Ana Rita Santos

Dear Thesis Examiners,

This letter is to inform you that Ms. Ana Rita Santos was a visiting graduate student under my supervision at Harvard University and the Broad Institute of Harvard and MIT for a period of 6 months. During this time Ms. Santos conducted a project applying diversity-oriented synthesis to the [2+2+2] cyclotrimerization of alkynes. Accordingly, the data that she presents in this thesis was wholly attributed to her independent efforts.

Respectfully,

Damian W. Young, Ph.D.

Group Leader-Chemical Biology Program

Acknowledgements

I would like to express my deep thanks to my supervisors Dr. Klaus Pors and Dr. Helen Sheldrake for giving me the opportunity to work on this interesting project which has allowed me to expand and develop my chemical and biological knowledge. I would also like thank them for the help they have provided during my PhD studies.

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I also would like to thank all my friends for all the support, care and friendship.

To my family a BIG THANK YOU for really everything, all the support in the good and bad moments, the care and above all the comprehension in accepting my decision of being far away from home to follow my dreams!

To Martin, my fofinho, thank you so much for always making me believe that I could get through this difficult stage of my life. Thank you for your understanding, love and friendship.

Abbreviations

Å – angstrom
Ac – acetyl
AIBN - azobisisobutyronitrile
AKT – serine/threonine-specific protein kinase
aq. – aqueous
Baib –bis(acetoxy)iodobenzene
B[a]P – benzo[a]pyrene
B/C/P – build/couple/pair
Bn –benzyl
Boc – *t*-butoxycarbonyl
BPDE – 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene
BTMSA – bis(trimethylsilyl)acetylene
Bu – butyl
^{n}BuLi – *n*-butyl lithium
Bz – benzoyl
Cbz – carbobenzyloxy/ benzyloxycarbonyl
CDP – chlorodiphenylphosphine
conc. – concentrated
COSY – correlated spectroscopy
Cp - cyclopentadiene
CYPs – cytochrome P450s
dAdo - deoxyadenosine
DBU – 1,8-diazabicycloundec-7-ene
DCE – dichloroethane
DCM – dichloromethane
DEAD – diethyl azodicarboxylate
DEPT – distortionless enhancement by polarization transfer
DFT – density functional studies
DiBAL – di*iso*butylaluminium hydride
DIC - 1,3-di*iso*propylcarbodiimide
DIPA - diisopropylamine
DIPEA - di*iso*propylethylamine
DIPHOS – 1,2-bis(diphenylphosphino)ethane
dGuo – deoxyguanosine
DMAP – 4-dimethylaminopyridine
DMDO – dimethyldioxirane
DME – 1,2-dimethoxyethane
DMF – *N*,*N*-dimethylformamide
DMP – Dess-Martin periodinane
DMPS - dimethylphenylsilyl
DMSO - dimethylsulfoxide
DNA – deoxyribonucleic acid
DPPE – 1,2-Bis(diphenylphosphino) ethane
DPPF – 1,1'-Bis(diphenylphosphino) ferrocene
DOS – diversity-oriented synthesis
EAS – electrophilic aromatic substitution
EBX – ethynyl-1,2-benziodoxol-3(1H)-one
Eq. – equivalent
ET - ecteinascidins
Et – ethyl
GAPDH - Glyceraldehyde 3-phosphate dehydrogenase
h – hour
HIF – hypoxia inducible factor
HMBC – heteronuclear multiple bond correlation
HMPA – hexamethylphosphoramide

HMQC - Heteronuclear Multiple-Quantum Correlation

HRMS – High Resolution Mass Spectrometry

HSQC – heteronuclear single quantum coherence spectroscopy

HTS – High Throughput Screening

IBX – 2-iodoxybenzoic acid

LAED – lithium acetylide ethylenediamine complex

LDA – lithium diisopropylamide

LG – leaving group

LHMDS – lithium hexamethyldisilazide

Ln – ligands

M – metal

m – *meta*

MAOS – Microwave Assisted Organic Synthesis

m-CPBA – *meta* chloroperbenzoic acid

Me – methyl

MeCN – acetonitrile

min – minutes

mp – melting point

Ms – methanesulfonyl (mesyl)

MTT – (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

NaHMDS – sodium hexamethyldisilazane

NBS – *N*-bromosuccinimide

NCI – National Cancer Institute

NCE – New Chemical Entity

NIS – *N*-iodosuccinimide

NMR –nuclear magnetic resonance

Ns – nosyl

o/n – overnight

PCC – pyridinium chlorochromate

Ph – phenyl

PhMe – toluene

PMA – phosphomolybdic acid

PMB – *p*-methoxy benzyl

ppm – parts per million

^{i}Pr – *iso*propyl

PTSA – *p*-toluenesulphonic acid

py – pyridine

PyAOP - (7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

R_f – retention factor

RNA – ribonucleic acid

RSM – recovered starting material

rt – room temperature

SAR – structure-activity relationship

sat. – saturated

SM – starting material

Sphos – 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl

tan δ – loss tangent

TBAF – tetra-*n*-butyl ammonium fluoride

TBDMS – *t*-butyldimethylsilyl

TCA – trichloroacetic acid

TEMPO - 2,2,6,6-Tetramethyl-1-piperidinyloxy

TFA – trifluoroacetic acid

THF – tetrahydrofuran

THIQ – tetrahydroisoquinoline

TIPS – triisopropylsilyl

TLC – thin layer chromatography

TMS– trimethylsilyl

TMSOTf – trimethylsilyl trifluoromethanesulfonate

TOS – target-oriented synthesis

Ts – tosyl

UPLC – ultra performance liquid chromatography

δ - chemical shift

Table of Contents

Chapter 1 Development of new methodologies to generate new chemical entities

1.1 Chemical biology as a recent field for the development of small molecules as new chemical entities

Chemical biology is a broad field of study that involves the multidisciplinary collaboration of synthetic organic chemists, medicinal chemists, computational chemists, molecular biologists, physicists, mathematicians, engineers amongst others. Although it does not present a simple definition, one can extrapolate that chemical biology is the use of chemical tools to uniquely interrogate human health and disease affording a much deeper knowledge of complex biological systems.[1,2]

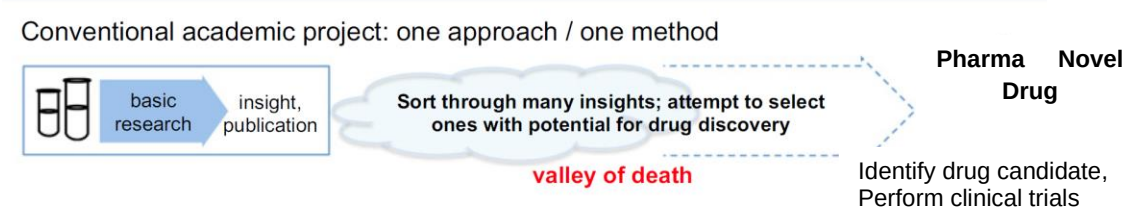


Figure 1 – Valley of death.[3]

Chemical biologists aim to identify small molecules that can target or modulate each of the individual proteins that are the cause of disease. As a field chemical biology aims to bridge basic and clinical research, which has been described as crossing over the so called “valley of death” (Figure 1). Significant work has been done by academic research groups to provide a better insight into complex biological systems and how pathways may be related. However from a pharmaceutical point of view, this research has not yet revolutionised validation of new targets and generation of new chemical entities (NCE) with therapeutic value.[3]

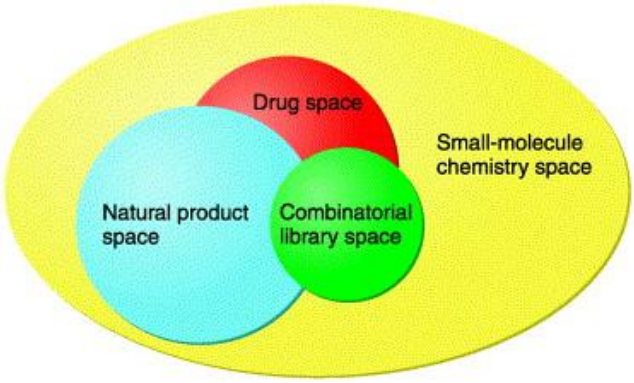
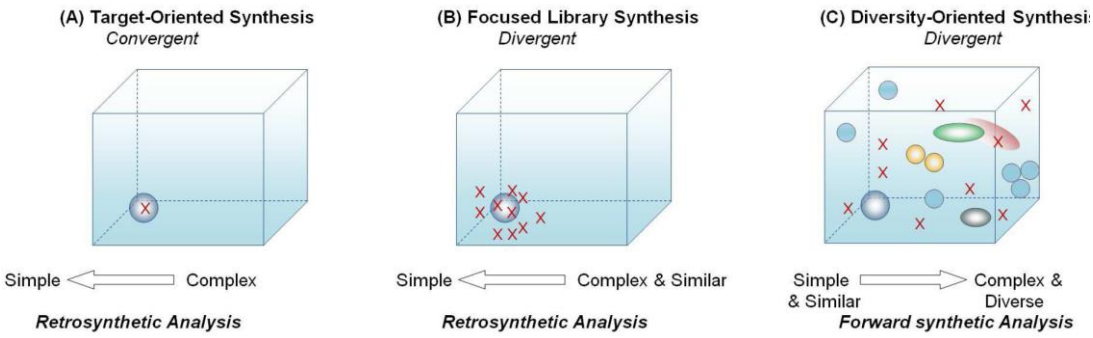


Figure 2 - A schematic representation of the overlap of chemical space occupied by natural products, drugs and combinatorial libraries in total small molecule chemistry space.[4]

It is believed that the chemical space encompasses 10^{60}-10^{200} molecules and it is proposed that screening new small molecules will cover more of the chemical space than natural products or molecules screened from high-throughput screening (HTS) approaches as depicted in Figure 2. Natural products and hits from HTS, in general, only cover a small amount of the chemical space due to the complexity of their structures, decreasing the chances of finding NCEs with true potential of being developed into drugs with clinical prospective.[5,6]

1.2 Diversity oriented synthesis – a strategy used by organic chemists and chemical biologists for small molecule synthesis



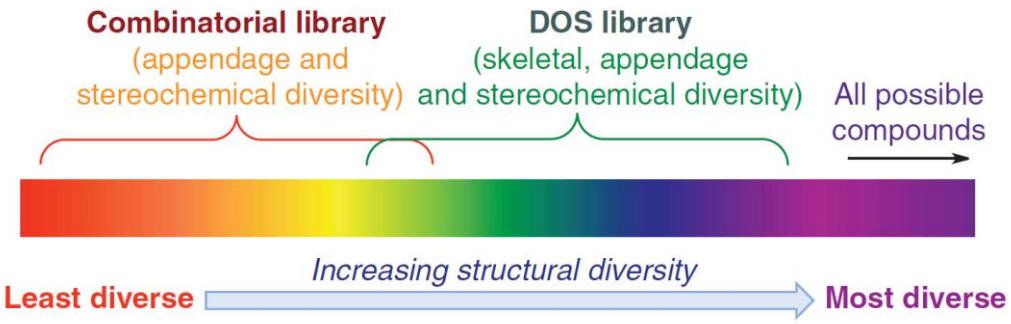


Figure 3 – Top: TOS and DOS focused library synthesis.[7] Bottom: The molecular diversity spectrum.[8]

Biologically active molecules have given chemists the challenge to develop efficient methods for their synthesis. Target oriented synthesis (TOS) and combinatorial chemistry have often been used for the design and synthesis of drug-like compounds that resemble natural products. Although these techniques provided a solid foundation for generating biologically active compounds, the chemical space they occupy is often very limited (Figure 3a).[9,10] TOS is based on a retrosynthetic approach (it moves in the direction of complex to simple), the objective is to synthesise the biologically active molecule (natural product or known drug) and closely related molecules; as shown in Figure 3a the chemical space is poorly populated. In combinatorial chemistry the synthesis is developed based on an active pharmacophore or scaffold, and medicinal chemists explore a certain region of the molecule that is known to provide the biological activity. Although this technique allows access to some degree of diversity, as Figure 3b illustrates, the chemical space covered is still not significant.

Accordingly, successful generation of truly NCEs may therefore not be achieved, and there is the demand for developing new and powerful methodologies for the synthesis of small molecules. Therefore, diversity-oriented synthesis (DOS) appeared as a new synthetic tool to synthesise broad libraries of small molecules with highly substituted scaffold diversity (skeletal and stereochemical), with the potential for encompassing several chiral centres, but with no single target.[10,11,9] This methodology is a divergent synthesis (contrary to the two methods described previously) that in a few steps (3-5), using robust synthetic methods, provides access to an immense number of different compounds leading to a highly populated chemical space (Figure 3c,

the synthesis moves from simple and similar to diverse and complex).[9] This method can either start with a building block (commercial or synthesised), which can be reacted with different reagents (branching pathway) or use different building blocks (commercial or synthesised) reacting with a common reagent (folding pathway). Regardless of the strategy used, the aim is to always provide a short, modular and diverse synthesis strategy.[7]

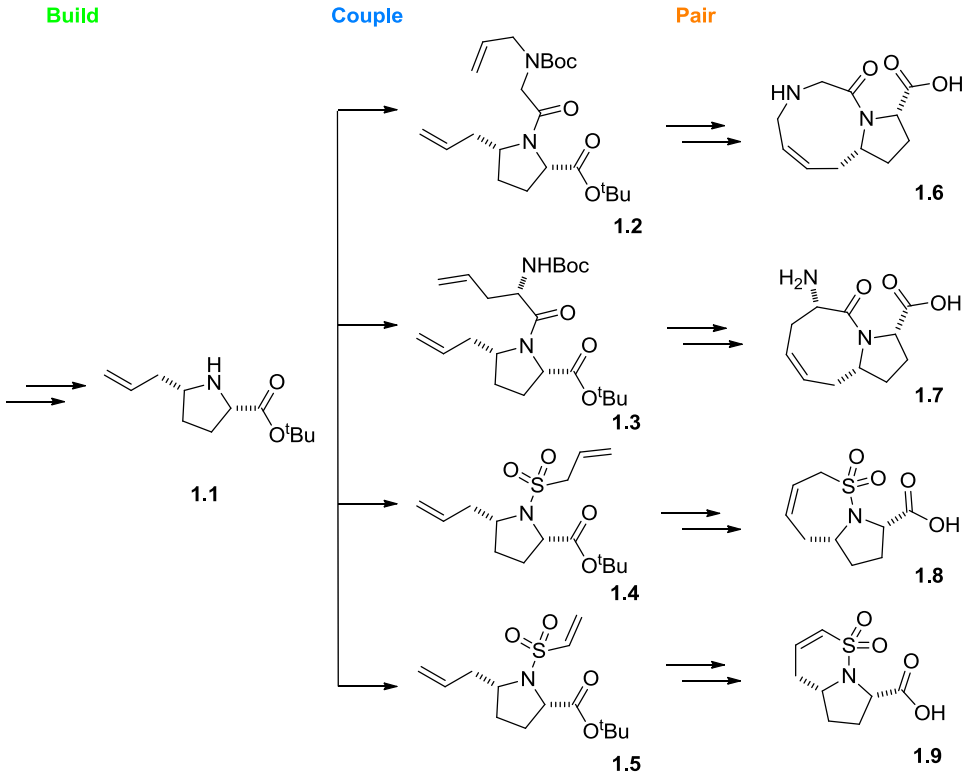


Figure 4 – Application of a B/C/P approach starting from proline 1.1 yielding bicyclic compounds 1.6–1.9.[12]

Despite all the advantages of this methodology, the original DOS approaches still afford molecules that mainly contain heterocyclic rings with a high number of sp^2 hybridisations. Therefore, there is the need to acess more diverse 3D molecules, i.e., with higher number of sp^3 hybridisations and better physical properties, in order to cover even more of the chemical space that may include more challenging unknown or "undruggable" targets. Consequently, within DOS the concept of the build/couple/pair (B/C/P) strategy was born (Figure 4).[12,13] The build phase involves obtaining stereochemically diverse building blocks (chiral, commercially available molecules are preferred) that have groups that can be further derivatised, i.e., that can be coupled intermolecularly with other building blocks (couple step) in order for all combinations of stereoisomers to be

covered. Finally, in the pair step the molecules are joined together intramolecularly, ideally using diverse reaction conditions (frequently transition metals (TM) catalysts) to form a higher number of products.

1.3 Tetrahydroisoquinoline alkaloids as a starting point for small molecules synthesis

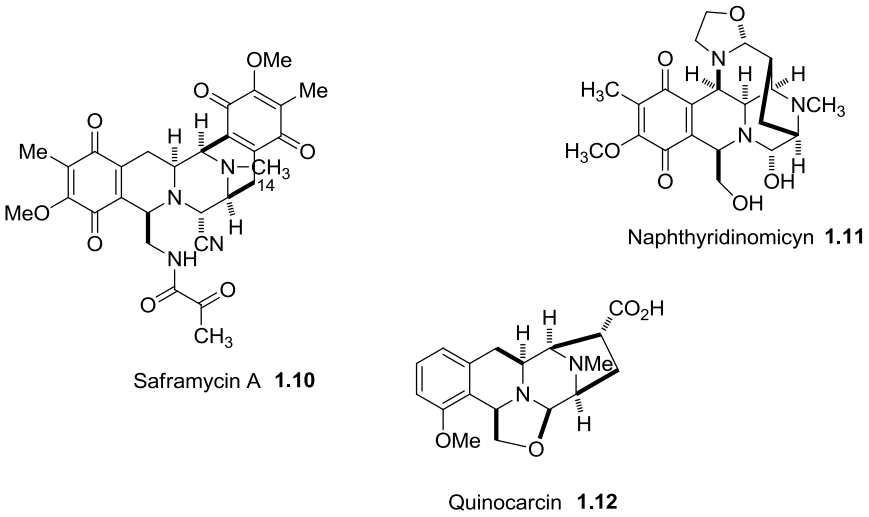


Figure 5 – Examples of a THIQ alkaloids.

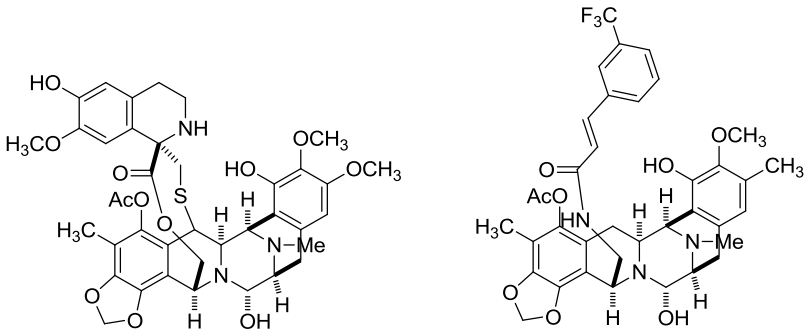
Tetrahydroisoquinoline (THIQ) alkaloids appeared as a class of anti-tumour antibiotics with the discovery of naphthyridomycin in 1974 by Kluepfel.[14] To date more than 60 compounds within this family have been isolated and biologically evaluated. THIQ alkaloids often possess both antimicrobial and anti-tumour activity, which is derived from a variety of different biological processes including: deoxyribonucleic acid (DNA) alkylation, DNA crosslinking, oxidative nucleic acid damage by superoxide formation and protein inhibition.[15]

The family of THIQ alkaloids as anti-tumour antibiotics can be divided into three different sub-classes according to their specific structural features: the saframycins (e.g. **1.10**), the naphthyridomycins (e.g. **1.11**) and the quinocarcins (e.g. **1.12**) (Figure 5).[15]

The saframycin family is the largest family and can be further subdivided into: saframycins, renieramycins, safracins and ecteinascidins. All the compounds belonging to this family share a core formed of five condensed six-membered rings, where the two terminal rings can exist as quinones and/or hydroquinones.

They also contain a THIQ motif and a piperazine ring, which shares the nitrogen with a second THIQ moiety. These molecules are sometimes also described as bis-tetrahydroisoquinoline structures.

Naphthyridomycins can be separated into two subfamilies with closely intertwined natural products: the naphthyridomycins/cyanocyclines/bioxalomycins and the dnacins/aclidomycins. Naphthyridomycins present a core of five to seven condensed rings, four six-membered rings and up to three five-membered rings. The aromatic component of the THIQ can also be present as a quinone moiety (tetrahydroisoquinoline-dione).



Yondelis® 1.13 **Zalypsis® 1.14**

Figure 6 – Yondelis® 1.13 and Zalypsis® 1.14.

THIQs anti-tumour antibiotics have a remarkable broad spectrum of biological activity, with Yondelis® (ET-743 **1.13**) and Zalypsis® **1.14** (PM00104) currently drawing most interest due to their ongoing clinical investigations as anticancer agents (Figure 6). The ecteinascidin-based ET-743 **1.13** was approved by the European Union in September 2007 for the treatment of advanced and metastatic soft-tissue sarcoma and in September 2009 for platinum-sensitive recurrent ovarian cancer in combination with Doxil,[16] it is currently approved in 56 countries within and outside the European Economic Area. Zalypsis® **1.14** is also a potent cytotoxic agent that displays high *in vitro* and *in vivo* antitumour activity in a wide variety of solid and haematologic tumour cell lines and human transplantable breast, gastric, prostate and renal xenografts tumours. It also binds to DNA but does not activate the DNA damage checkpoint. Thus, Zalypsis **1.14** exerts cytotoxic effects dependent on DNA binding, but that is not

associated with DNA damage *per se*.[17] Zalypsis **1.14** is currently in Phase II clinical trials for endometrial and cervical cancer.[18]

The last family of the THIQs anti-tumour antibiotics is the quinocarcin family, which can be divided into three subfamilies: quinocarcin itself, tetrazomine and lemonomycin. This family of natural products contains a tetracyclic core, also bearing the characteristic isoquinoline fragment, a piperazine moiety and a condensed five-membered ring. The aromatic part can also exist as a quinone or a hydroquinone.

1.3.1 Quinocarcin family

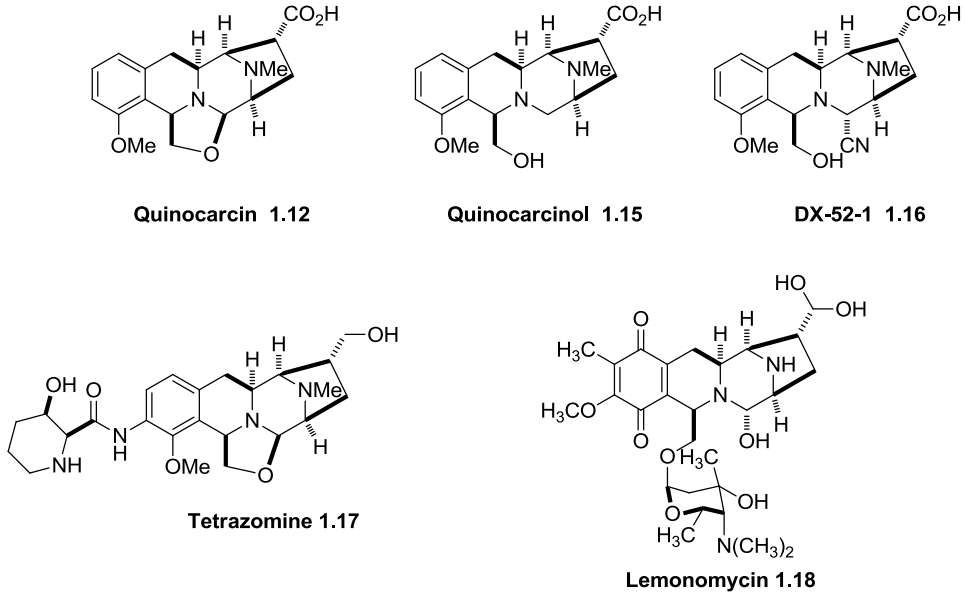


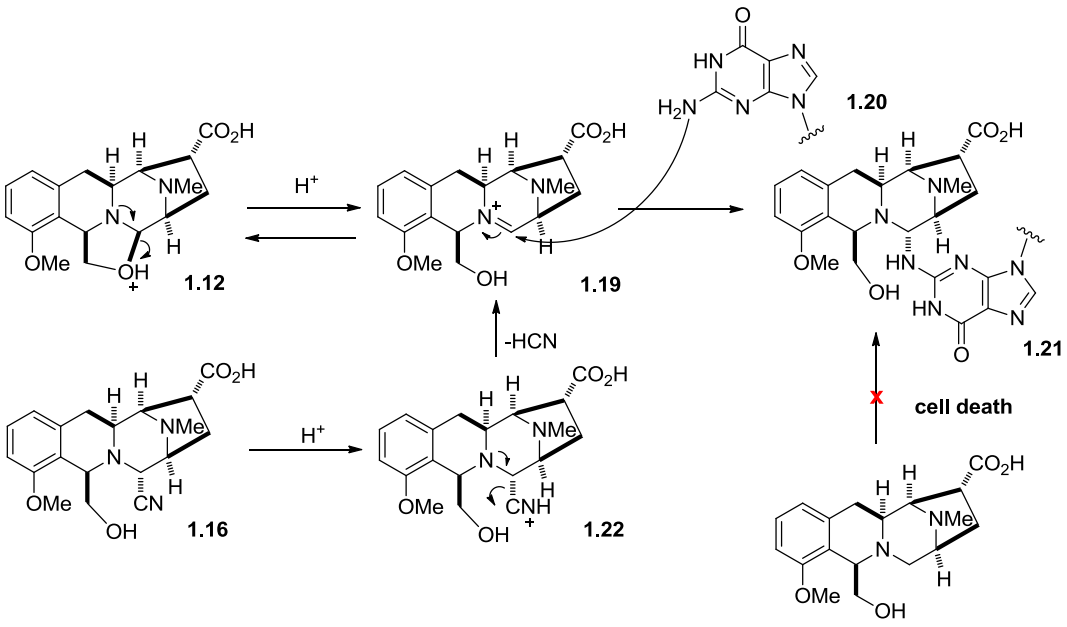
Figure 7 – Examples of THIQs anti-tumour antibiotics belonging to the quinocarcin family.

Quinocarcin **1.12** (DC-52) is the THIQ anti-tumour antibiotic with the simplest structure and, as a consequence, has often been used as the starting point for exploring the chemistry of these biological compounds (Figure 7).

The biological activity of quinocarcin has been demonstrated against Gram positive bacteria, *Staphylococcus aureus*, *Bacillus subtilis* and *Klebsiella Pneumoniae* and against P388 lymphocyte leukaemia in mice.[19] As an anti-tumour antibiotic it appears to inhibit ribonucleic acid (RNA) synthesis over DNA and protein synthesis.[19] Its monocitrate derivative (KW2152) and its cyano

derivative **1.16** (DX-52-1) were the first agents identified by the National Cancer Institute (NCI) for displaying activity against the 60 human cancer cell line panel.[20] KW2152 showed potent anti-tumour activity against St-4 gastric carcinoma, Co-3 human colon carcinoma, MX-1 human mammary carcinoma, M5057 sarcoma, B16 melanoma and P388 leukaemia.[21] KW2152 underwent Phase I clinical trials in Japan, but failed due to toxicity following daily treatment. The more stable analogue, DX-52-1 **1.16** underwent Phase I clinical trials in the USA, however this analogue was also abandoned due to gastrointestinal toxicity.[22]

More recently, it has been shown that DX-52-1 **1.16** and KW2152 can also target Hypoxia Inducible Factor-1 (HIF-1), a transcriptional factor which is induced under low levels of oxygen and is crucial for tumour progression, invasion and metastasis.[23,24] DX-52-1 **1.16** also appears to inhibit cell migration, which is common to both normal cells and cancerous cells and is required for a range of biological responses including embryonic development, tissue repair, immune cell function, inflammation, angiogenesis, cancer cell invasion and metastasis. Recent studies have shown that DX-52-1 **1.16** targets the membrane-cytoskeleton linker radixin followed by binding the multifunctional carbohydrate-binding protein galectin-3. The targeting of galectin 3 seems to be *via* formation of a covalent bond between DX-52-1 **1.16** and the C-terminal region of radixin, causing radixin to dissociate from actin.[25,26]

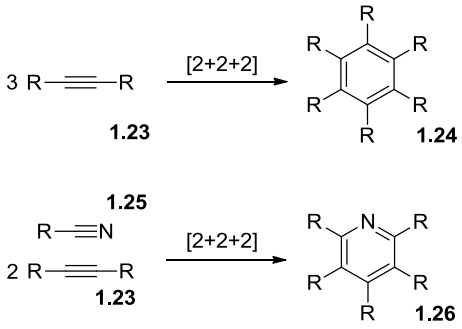


Scheme 1

The antiproliferative effect of quinocarcin **1.12** and DX-52-1 **1.16** could be explained through a DNA alkylation event *via* an iminium ion **1.19**. The presence of an unstable oxazolidine at C7 would allow formation of an electrophilic iminium intermediate **1.19** in a similar fashion to DX-52-1 **1.16** (Scheme 1).[15] It was proposed that the iminium ion could be attacked by the N2 residue of guanine **1.20**, forming a covalent bond generating adduct **1.21** as shown in Scheme 1. The alkylation would occur *via* protonation of the nitrile group or by ring opening of the oxazolidine. Despite the proposed mechanism of action, DNA alkylation *via* the iminium ion intermediate has never been substantiated experimentally.

Quinocarcinol **1.15** which does not possess the oxazolidine component or the nitrile (Scheme 1) is devoid of biological activity.[27] This provides an opportunity for bioprecursor development by targeting cytochrome P450s (CYPs) overexpressed in cancer tissues including CYP1A1, 1B1, and 2W1 (which will be further discussed in Chapter 4). Recent reports by Patterson, Pors and co-workers show duocarmycin bioprecursors to be selectively activated by CYP1A1[28] and CYP2W1[29] in bladder and colorectal cancer tissues, respectively. Similarly, quinocarcinol **1.15** may be a suitable substrate for CYP-bioactivation in cancer tissues and is in part subject to investigation in this thesis (Chapter 4).

1.4 Transition-metal mediated [2+2+2] cyclotrimerisations of alkynes and nitriles



Scheme 2

[2+2+2] cyclotrimerisation of alkynes and nitriles has appeared as a new methodology for the synthesis of carbon and heterocyclic benzene derivatives (Scheme 2) as an alternative to the electrophilic aromatic substitution (EAS) or *ortho*-metallation.[30,31,32,33,34,35]

The first report of [2+2+2] cyclotrimerisations dates back to 1866 when Berthelot described the cyclisation of acetylene to yield benzene at 400 ºC. Despite the reaction being exothermic, the reagents need to overcome a large entropic barrier when associating three molecules, which gives rise to the need for such high reaction temperatures.[31] These harsh conditions precluded alkyne cyclisation methodology from being applicable to a wider range of molecules. Consequently, in 1948 Reppe developed the use of transition-metals, demonstrating for the first time the use of a Ni catalyst for the synthesis of benzene from acetylene.[36]

In the last 60 years, research has advanced sufficiently to allow the use of a diversity of transition-metals, which nowadays includes at least 17 different metals.[33] The main ones used in [2+2+2] cyclotrimerisations are Co, Rh, Ru, Ni, Pd, Ti, Ir, Pd and Zr, with the cobalt catalysts the most explored and widely used.[37,38,34,39,40,41,42]

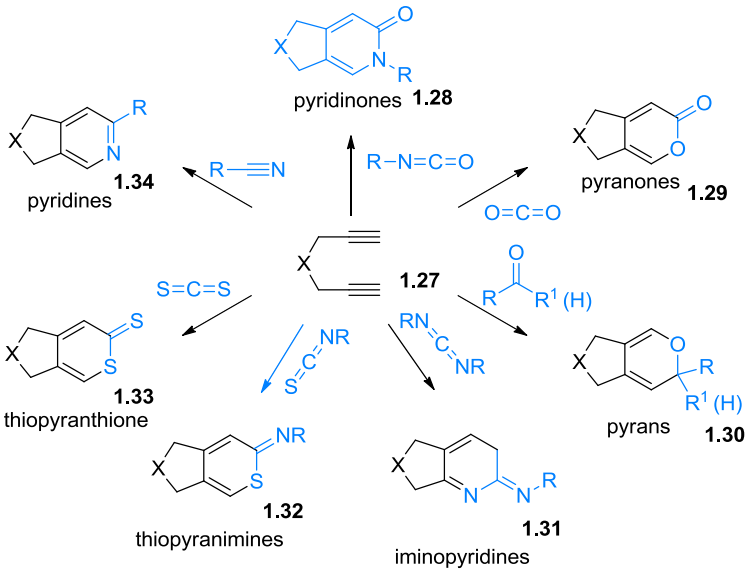


Figure 8 – [2+2+2] cyclotrimerisation of dialkynes with an unsaturated molecule.

More advances within the field led to similar reactions where one of the alkyne contributors is replaced by another unsaturated substrate including nitriles, isocyanates, alkenes, imines, isothiocyanates leading to diverse and highly

substituted 6-membered ring derivatives (pyridines, pyridones, thiopyridones, 1,3-cyclohexadienes, iminopyridines, indolizidinespyrones, etc) (Figure 8).

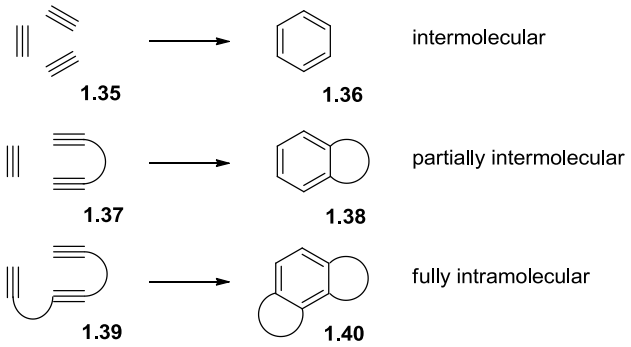


Figure 9 – Different types of [2+2+2] cyclotrimerisations of alkynes and tethered alkynes.

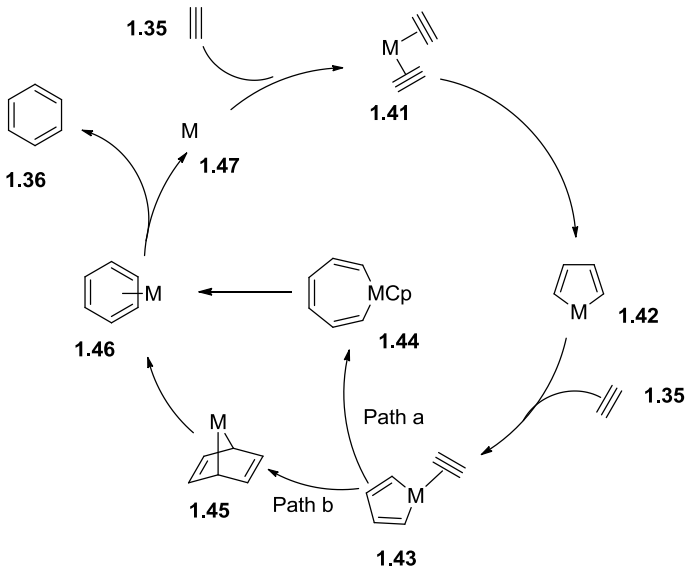
There are three different types of [2+2+2] cyclotrimerisations of alkynes, and alkynes and another unsaturated substrate (Figure 9). To simplify the explanation the types of cyclotrimerisations will only refer to alkynes, but the same applies to heteroatom containing compounds. Intermolecular cyclotrimerisations happen between three distinct alkynes, while in partially intermolecular reactions only two alkynes are tethered. In fully intramolecular cyclotrimerisations a single molecule contains all three alkynes.

Transition-metal mediated [2+2+2] cyclotrimerisations of alkynes is an elegant and versatile convergent tool for the construction of densely (poly)substituted benzene products and related heterocyclic derivatives, although less is known about the latter. It is a very important reaction in terms of atom economy, because it involves the formation of several C-C or C-heteroatom bonds in a single step. It is also possible to synthesise chiral systems using chiral transition metal complexes as catalysts,[33,35] however this topic will not be covered in the present work.

Emerging evidence indicates that [2+2+2] cyclotrimerisations have a wide application in both academia and industry, mainly in the synthesis of various organic compounds such as cyclophanes, biaryls, organophosphorus compounds, helicene-like molecules, organic materials and complex biologically active compounds (see section 1.4.3).[34]

1.4.1 Transition-metal catalysed [2+2+2] cyclotrimerisation reactions for benzene derivatives

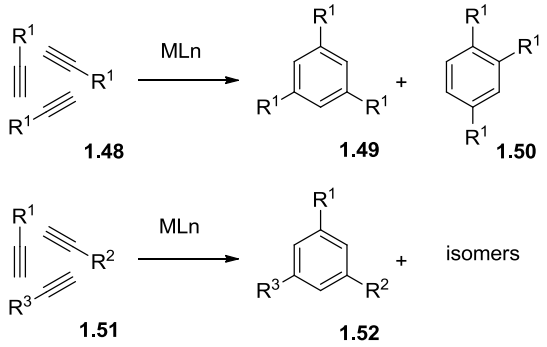
1.4.1.1 Mechanism



Scheme 3

The mechanism for the transition-metal catalysed [2+2+2] cyclotrimerisations of alkynes depends significantly on the metal of the catalyst, the ligands and substrate. The generally accepted mechanism that describes these types of reactions is shown in Scheme 3. Initially, two molecules of alkyne coordinate with the catalyst surface (**1.41**), then by oxidative coupling the metallacyclopentadiene adduct **1.42** is formed. The third alkyne coordinates with the metal centre and here the reaction can be driven in two directions (depending on the metal). The metallacyclopentadiene adduct **1.43** can react in a Diels-Alder fashion [4+2] cycloaddition (path b) to form adduct **1.45**, which happens for example with cobalt based catalysts.[33] Alternatively the third alkyne can insert at the M-C bond with ring expansion leading to the formation of complex **1.44** (path a) which happens with ruthenium catalysts.[43] The final benzene **1.36** is then formed by reductive elimination of either complexes **1.44** or **1.45** followed by metal de-coordination with recovery of the catalyst **1.47**.

1.4.1.2 Regio- and chemoselectivity

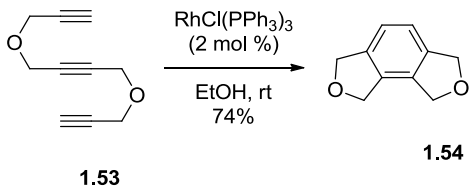


Scheme 4

In the [2+2+2] cyclotrimerisations the regio- and chemoselectivity is a major problem, paticularly in the intermolecular trimerisation, where typically mixtures of products are formed (Scheme 4).

The chemo- and regioselectivity can be controlled in two steps: first during the formation of the metallacyclopentadiene adduct **1.42** and secondly during the insertion of the third alkyne component.

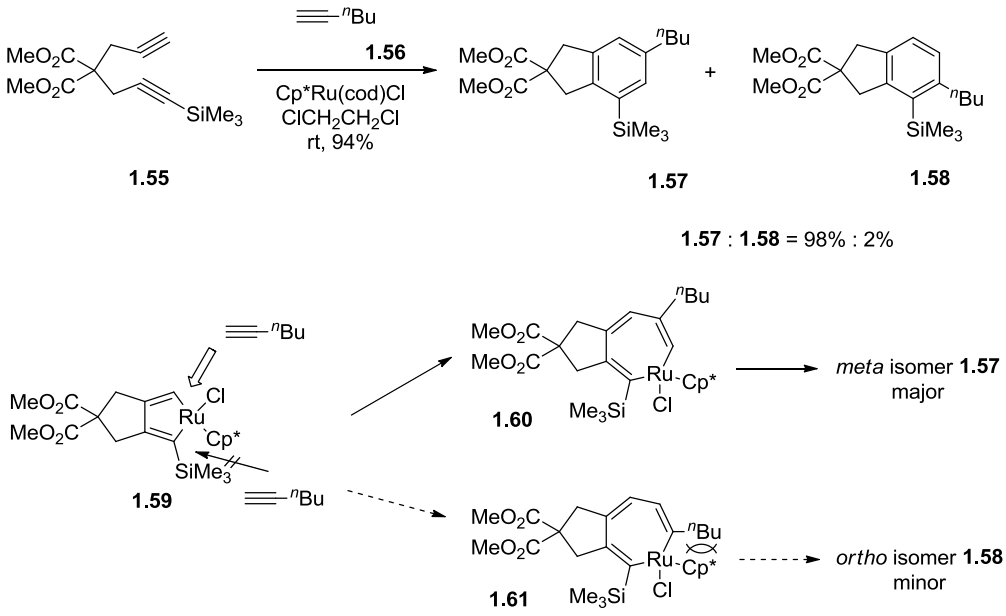
Chemoselectivity depends on the ability of the catalyst to preferentially coordinate with the first two alkynes *vs* the third: alkynes with similar electronic and steric properties will react in a similar way. Initially, to avoid the formation of regioisomers, stoichiometric amounts of catalyst have been used with the third alkyne added at the end, thus forcing the first two alkynes to bind to the catalyst before the third is introduced.[44] However, such methods are unattractive due to the cost of the catalysts and low yields obtained, and chemoselectivity still remains a challenge. In the partially intramolecular approach, there is still the potential for dimerisation of the diyne but large amounts of monoalkyne and diluted solutions of the reaction mixtures are often used in order to reduce the likehood of dimerisation.



Scheme 5

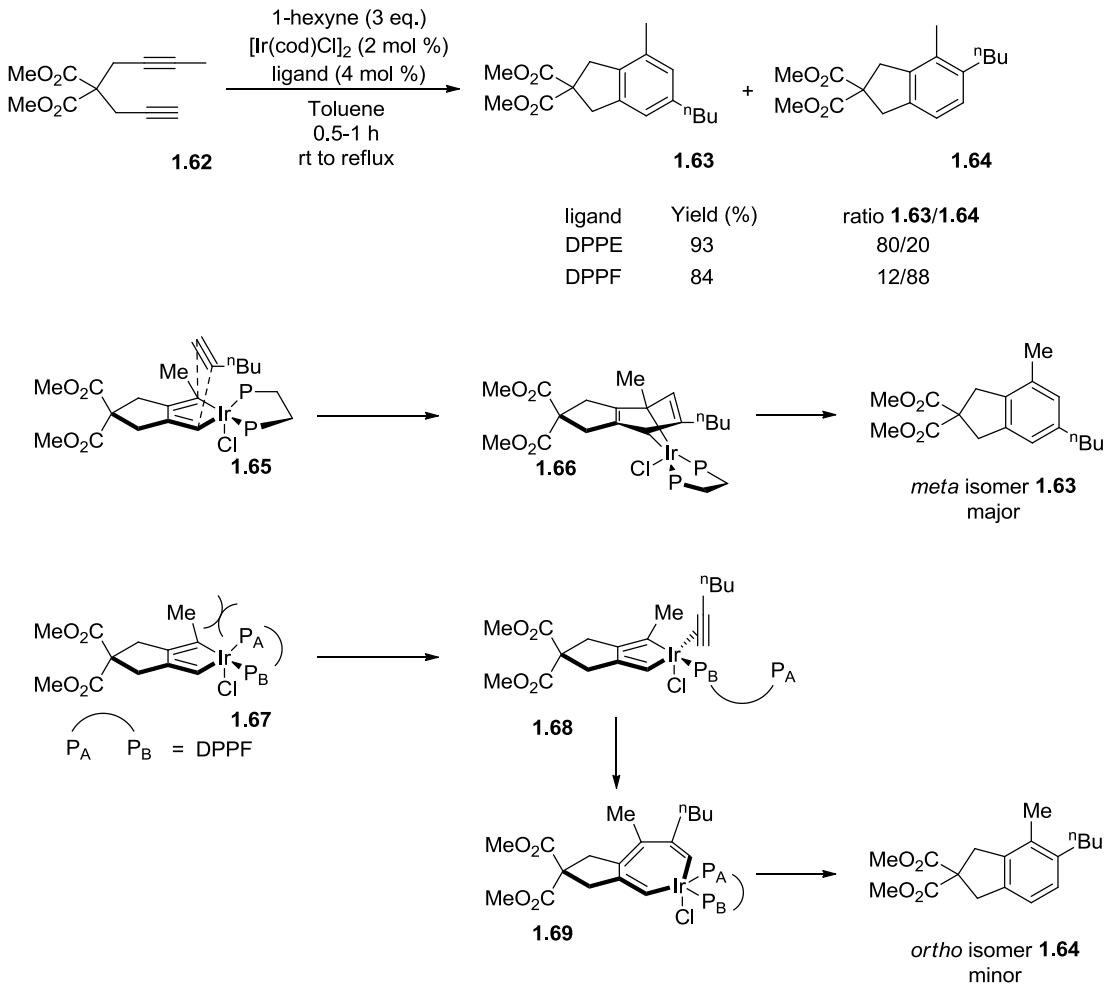
Regioselectivity depends on the orientation of insertion of the third alkyne and isomers can be formed if it is not symmetric. Some useful strategies have emerged to overcome this problem, for example full control of regioselectivity can be obtained through a fully intramolecular reaction (Scheme 5).[45] Usually only one isomer is obtained, since other isomers would result in a highly strained ring system.[46]

Regioselectivity can be obtained in a partially intramolecular way affording a bicyclic product. Selected examples are described below (for reviews see[30,31,32,33,34,35]).



Scheme 6

In order to avoid isomer formation in a partially intramolecular reaction, a group can be added to the diyne that directs the addition of the alkyne, which can induce regioselectivity by steric hindrance. Dialkyne **1.55** reacts with monoalkyne **1.56** in the presence of Cp*Ru(cod)Cl to give products **1.57** and **1.58** with *meta*/*ortho* selectivity 98:2 (Scheme 6). The bulky Cp* group directs the insertion of the monoalkyne in the less substituted Ru-C bond (Scheme 6), therefore avoiding a steric clash between the butyl group and the Cp* group.[47]



Scheme 7

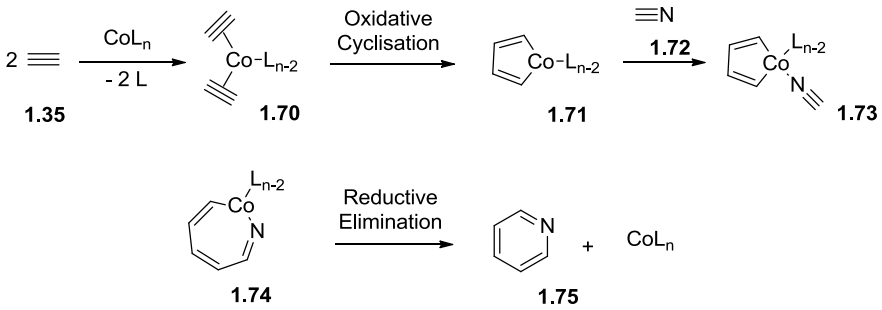
The ligand on the catalyst can also play an important role in isomer formation. An example is illustrated in Scheme 7, where the use of 1,2-bis(diphenylphosphino)ethane (DPPE) favours the *meta* regioisomer while 1,1'-bis(diphenylphosphino)ferrocene (DPPF) favours the *ortho* regioisomer.[41] When DPPE is used the reaction has been proposed to occur *via* a Diels-Alder pathway (Scheme 7, complex **1.66**). Bidentate coordination of DDPE affords a 5-membered ring which gives the most stable chelation, allowing for the coordination of the monoalkyne to happen above the plane (complex **1.65**). The *meta* isomer is more favoured due to less steric hindrance with the methyl group. On the other hand, when DPPF is used the reaction follows the ring expansion pathway (complex **1.69**). DPPF has a large bite angle, therefore when the iridium catalyst coordinates with dialkyne **1.62** to form metallacyclopentadiene **1.67** a steric clash between the methyl and the PPh_2 groups will force the complex to dissociate, allowing for the formation of a

vacant site on the iridium centre for monoalkyne coordination (complex **1.68**). In this situation the *ortho* isomer is more favoured because the iridium complex is bulkier than the methyl group.

1.4.2 Transition-metal catalysed [2+2+2] cyclotrimerisation reactions for pyridine derivatives

Transition-metal catalysed [2+2+2] cyclotrimerisations to form pyridine derivatives involves the reaction of two alkynes with a nitrile. This reaction was first reported by Wakatsuki and Yamazaki in the early 1970s, where a Co catalyst was used in a stoichiometric amount.[48] Nowadays this reaction uses a substoichiometricamount of a wide range of transition-metals.[34,35,49,50]

1.4.2.1 Mechanism

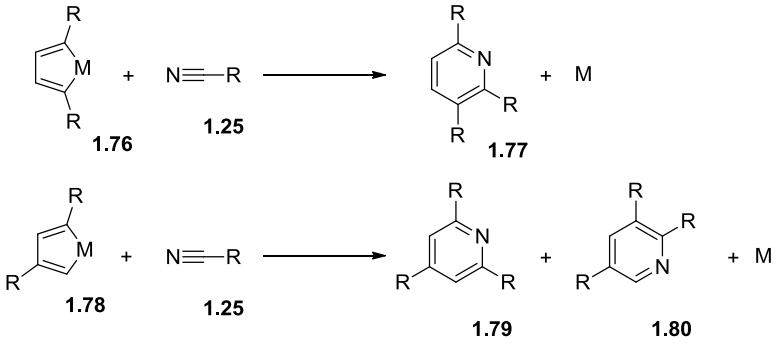


Scheme 8

The mechanism of the cyclotrimerisation to give pyridine derivatives is very similar to the one described above for benzene derivatives (section 1.4.1.1). The cycle starts with coordination of two alkynes to the transition-metal to form the metallacyclopentadiene **1.71** by oxidative coupling. The next step involves coordination of the nitrile **1.73** followed by insertion into the M-C bond leading to the formation of the azametallacycloheptatriene **1.74**, which undergoes reductive elimination to give the desired pyridine derivative **1.75** (Scheme 8).

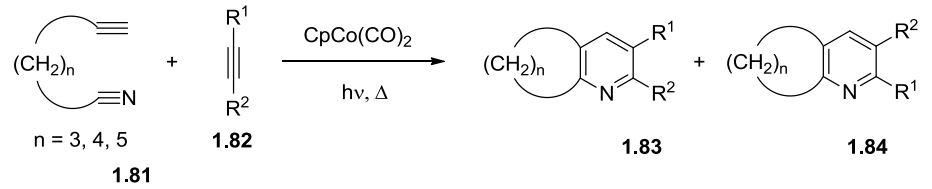
1.4.2.2 Regio- and chemoselectivity

In the [2+2+2] cyclotrimerisations of alkynes and nitriles there will always be competition between the alkyne cyclotrimerisation and pyridine formation. In order to avoid alkyne cyclotrimerisation, a large excess of the nitrile is usually used. The catalyst of choice can play an important role in the chemoselectivity, as the ligand can predetermine which reactant coordinates first. Nitrile trimerisation is generally less favoured due to the instability of the diazametallacycle that would be formed. Nitrile trimerisation is also much slower than the formation of the desired product or the trimerisation of the alkyne. There is still the possibility for the initial coordination of the metal to an alkyne and a nitrile *via* intermolecular reactions, but density functional theory (DFT) studies have shown that this pathway is very unlikely.[35]



Scheme 9

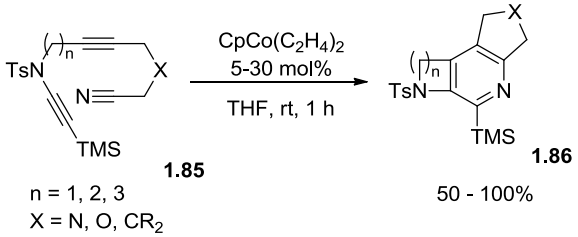
Intermolecular reactions usually lead to mixtures of products (Scheme 9) and the formation of isomers depends on the chemoselectivity of the catalyst in the oxidative step. Theoretically, the insertion of the nitrile can take place in two orientations, however, experimentally it is observed that the nitrogen atom is placed near the bulkiest group.[50] The same applies for tethered dialkynes and alkynenitriles, where the bulkiest group is placed near the nitrogen (Scheme 10 and Table I).[50]



Scheme 10

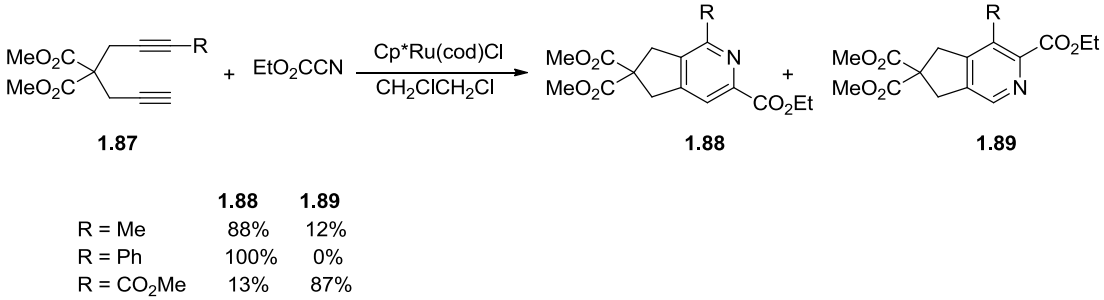
n	R^1	R^2	Yield (%)[a]	Product ratio (1.83:1.84)
3	Me	Me_3Si	70	>95:1
4	CO_2Me	Me_3Si	82	1.1:1
4	CO_2Me	Et_3Si	78	1:1
4	CO_2Me	$^iPr_3Si$	67	1.7:1
4	$CONEt_2$	Me_3Si	87	1.4:1
4	OMe	Et_3Si	43	>95:1
4	H	Et_3Si	26	>95:1
4	Me	Me_3Si	70	>95:1
5	Me	Me_3Si	66	>95:1

Table I –Regioselectivityfor the cyclotrimerisation of alkynenitrile 1.81 with different unsymmetric monoalkynes. [a] combined yield.



Scheme 11

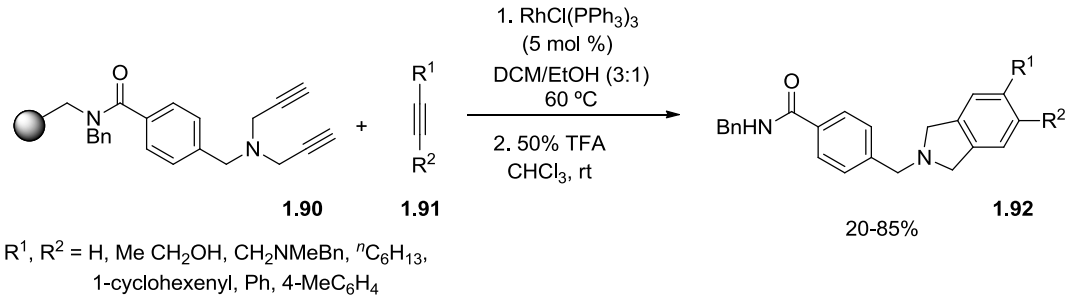
Completely intramolecular reactions are generally associated with greater regiocontrol (Scheme 11).[51]



	1.88	1.89
R = Me	88%	12%
R = Ph	100%	0%
R = CO_2Me	13%	87%

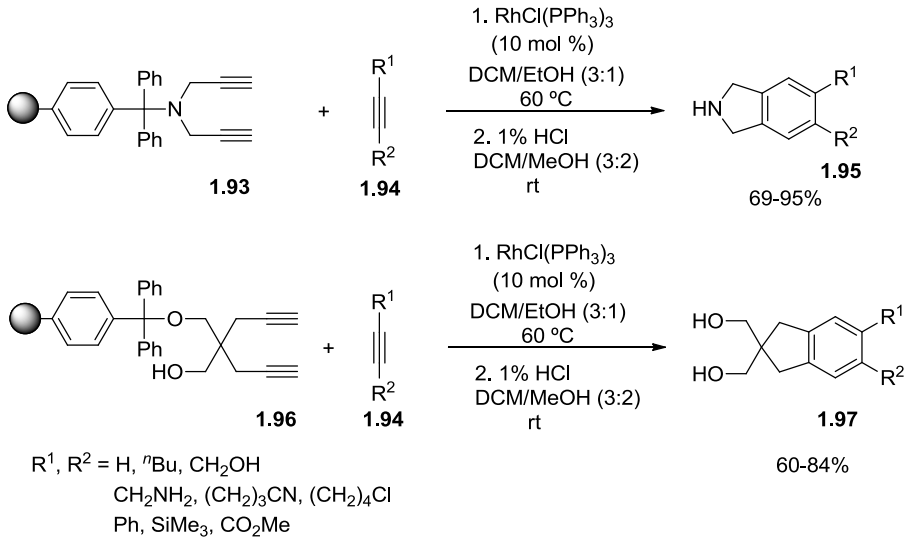
Scheme 12

The cyclotrimerisation of tethered dialkynes and alkynenitriles also depends strongly on the electronics of the tethered component, i.e., electron deficient alkynes will react with the electron rich carbon from the nitrile and *vice versa* (Scheme 12).[52]



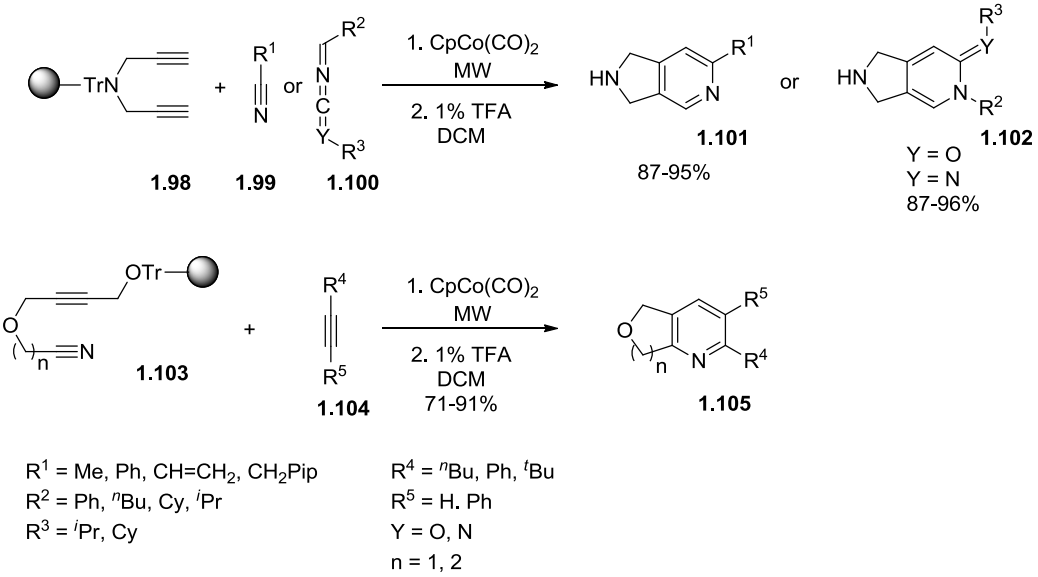
Scheme 13

Recently, a new strategy has been developed to overcome this regio- and chemoselectivity problem through spatial separation of the substrates by adsorption of the diyne onto a solid resin. This solid-phase methodology is a great tool for the construction of small libraries for combinatorial chemistry, and permits easy automation, parallelisation and purification. The first example of this approach was carried out by Sun and co-workers for the construction of a variety of isoindolines catalysed by Wilkinson's catalyst ($RhClP(Ph_3)_3$), Scheme 13.[53]



Scheme 14

Deiters and co-workers carried out a more thorough study, initially using Wilkinson's catalyst and a broad variety of substrates (examples can be seen in Scheme 14).[54]



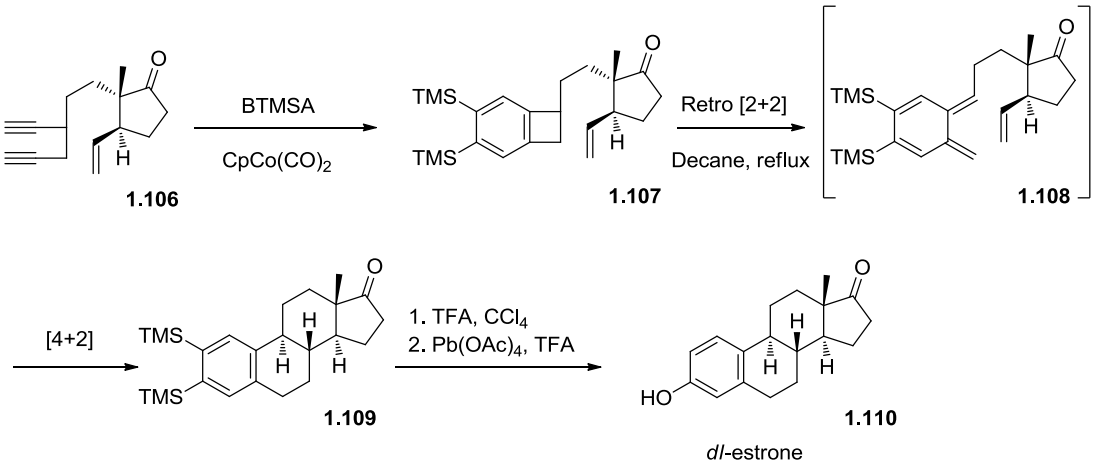
Scheme 15

Later, the same group used Vollhardt's catalyst to study different immobilisation strategies using different diynes with different unsaturated molecules (alkynes, nitriles, carbodiimides and isocyanates) (Scheme 15).[55] This also involved the development of microwave-assisted [2+2+2] cyclotrimerisation reactions, which will be the subject of investigations in Chapter 3.

In summary, there is emerging evidence that [2+2+2] cyclotrimerisations of alkynes and other unsaturated molecules can be used for facile access to highly functionalised (poly)substituted carbo- and heterocycles, that might not be possible by other synthetic methodologies. It is a complementary strategy to the well-known Diels-Alder reaction and permits the synthesis of one-, two- or three-membered ring(s) in a single step, which tolerates different functional groups such as alcohols, amines, alkenes, ethers, esters, halogens and nitriles to be used.[32] Finally, regio- and chemoselectivity strongly depends on the reactants presented in the reaction mixture and hence provides a tool for controlling the diversity of the target molecules.

1.4.3 Applications of the transition-metal mediated [2+2+2] cyclotrimerisations in natural product synthesis

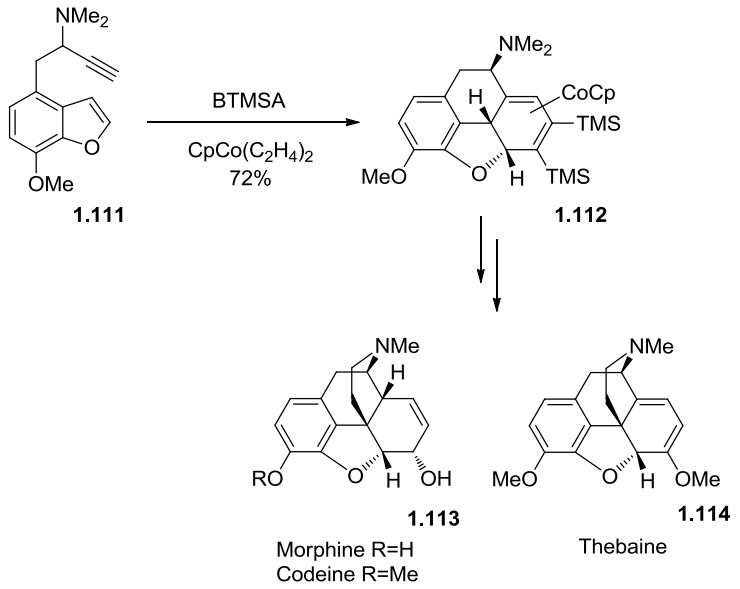
The implementation of the transition-metal catalysed [2+2+2] cyclotrimerisation of alkynes with other unsaturated molecules is increasingly being employed as a part of the "synthetic chemistry toolbox". This approach can be incorporated into a variety of syntheses including organic compounds such as cyclophanes, biaryls, organophosphorus compounds, helicene-like molecules, supramolecular and polymer chemistry and natural product synthesis.[34] Natural products and their derivatives are rich in highly functionalised aromatic rings and their syntheses are often long, cumbersome and with low yields. [2+2+2] cyclotrimerisations have the ability to form mono-, bi- and tricyclic systems in a single step as described previously; therefore they may provide an advantage in key steps of syntheses towards natural products. A few examples of the synthesis of natural products and derivatives that use this methodology are described below.



Scheme 16

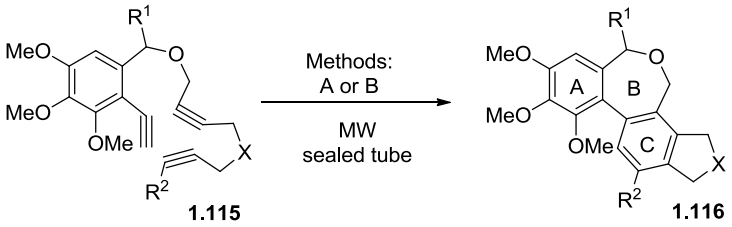
One of the first applications of [2+2+2] cyclotrimerisations applied to natural product synthesis was reported by Vollhardt[56] during the synthesis of the steroid estrone **1.110** (Scheme 16) based on the cyclotrimerisation of 1,5-hexadiene **1.106** and bistrimethylsilylacetylene (BTMSA) catalysed by $CpCo(CO)_2$ affording **1.107** which underwent retro [2+2] to afford estratrienone **1.108,** followed by Diels-Alder cycloaddition under the reaction conditions to give

tetracycle **1.109** in 71% yield. Consequent treatment of **1.109** with trifluoroacetic acid (TFA) and lead acetate afforded estrone **1.110**.



Scheme 17

Vollhardt's group over the years has made a strong contribution to the application of [2+2+2] cyclotrimerisations. For example, they developed a novel strategy for morphinoid derivatives such as morphine, codeine and thebaine, where the key step involves a [2+2+2] cyclotrimerisarion of furan derivative **1.111** with BTMSA catalysed by $CpCo(C_2H_4)$ to form the tetracyclic core of these alkaloids (Scheme 17).[57]

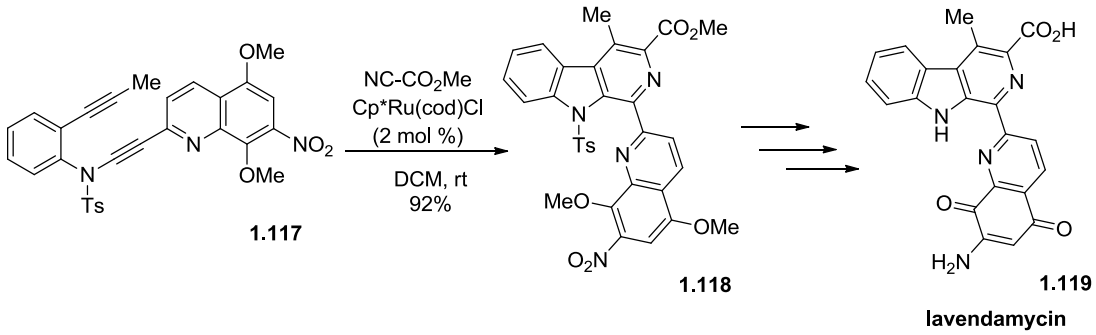


A: $RhCl(PPH_3)_3$ (10 mol %), toluene, 80 ºC (300 W), 30 min
B: $CpCo(CO_2)$ (20 mol %), PPh_3 (40 mol %), chlorobenzene, 150 ºC (300 W), 30 min

Scheme 18

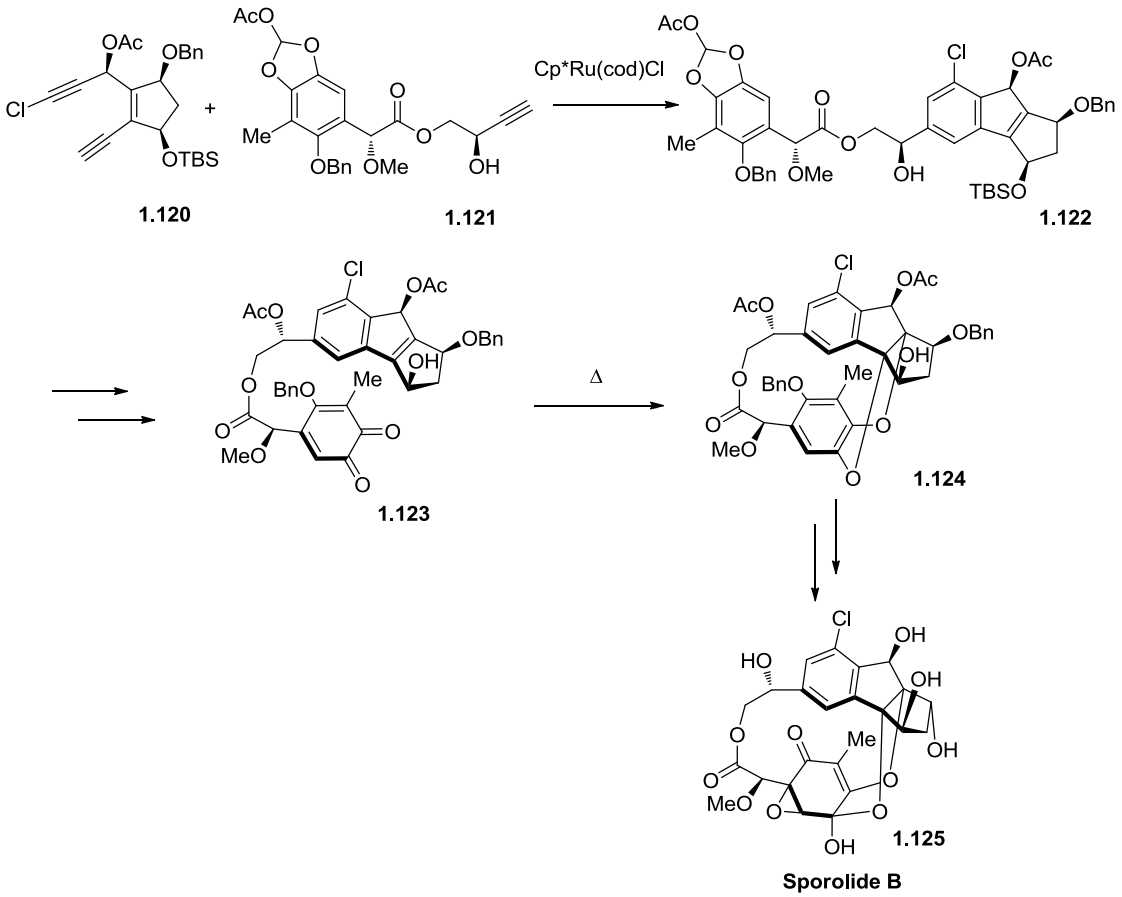
Another example of the application of this methodology is in the synthesis of colchicinoids. Colchicine, a natural compound with anticancer properties,

possesses an interesting ABC tricyclic pharmacophore, which makes these type of compounds very attractive for biological screening. An example is the synthesis of colchicine derivatives, 6-oxa-allocolchicinoids **1.116**, that have been obtained through a fully intramolecular reaction of triyene **1.115** catalysed by Wilkinson's or Vollhardt's catalyst under microwave irradiation (Scheme 18); subsequent analysis of these [2+2+2] cyclotrimerised colchicine alkaloids showed they possess the capacity to induce apoptosis.[58]



Scheme 19

The key step in the synthesis of the indole-based anti-tumour antibiotic lavendamycin **1.119** (Scheme 19) is the construction of fused pyrrole and pyridine rings, which have been generated *via* [2+2+2] cyclotrimerisation from the reaction of 1,6-diyene **1.117** and methyl carbonocyanidate and catalysed by Cp*Ru(cod)Cl, in an elegant regioselective approach (Scheme 19).[59]



Scheme 20

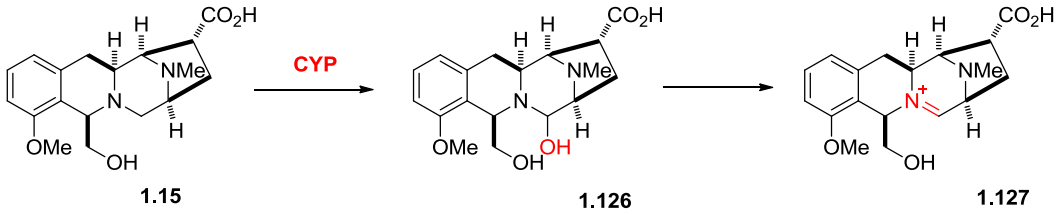
Nicolaou's group devised a strategy which implemented transition-metal catalysed [2+2+2] cyclotrimerisation in the synthesis of Sporolide B **1.125** (Scheme 20).[60] The regio- and stereocontrolled synthesis of this unusual 24-carbon polycyclic structure involves, in one of the key steps, a [2+2+2] partially intramolecular cyclotrimerisation of alkynes catalysed by Cp*RuCl(cod) to form the indene motif (Scheme 20). The other remarkable key step in this synthesis is the Diels-Alder cycloaddition to close the macrocycle.

Other compounds with biologically important properties have been synthesised using this [2+2+2] approach, which will not be discussed here, that include anthraquinones,[61] protoberberines,[62] taxanes,[63] camptothecin,[64] sesquiterpenes,[65,66] steroids,[67] unnatural α-amino acids and peptides.[43,68]

1.5 Rationale

As chemical biology becomes more integrated in drug discovery there is a greater demand for new and efficient strategies for the synthesis of small molecules to target different biological pathways (section 1.1).

The quinocarcins have been shown to interfere with the HIF-1 pathway, cell migration and DNA alkylation by quinocarcin salt (KW2152) and DX-52-1 **1.16**. The lack of activity of quinocarcinol **1.15** is interesting and may provide a route to bioprecursors development with potential for cancer drug development (Scheme 21). CYPs might selectively hydroxylate quinocarcinol to compound **1.126** which can lead to iminium ion **1.127** by loss of water. Nonetheless, the lack of knowledge in understanding the biological activity of the quinocarcins provides a reason why further exploration of this family of compounds is necessary. As a consequence, the design and synthesis of new truncated quinocarcin analogues, similar as well as diverse, could be used to probe the biological targets and/or pathways to aid in elucidating structural fragments responsible for their biological activity.



1.15 **1.126** **1.127**

Scheme 21

There are several syntheses reported for the preparation of THIQs anti-tumour antibiotics; most of the methods reported are based on the traditional methods for THIQ synthesis including implementation of the Bischler-Napieralski and the Pictet-Spengler ring closure reactions where the aryl ring and its substitution pattern is set prior to the cyclisation step.[15,69,70,71,72,73,74] Such methods are generally not amenable to concurrent total synthesis and simultaneous library preparation of the natural products and more diverse derivatives.

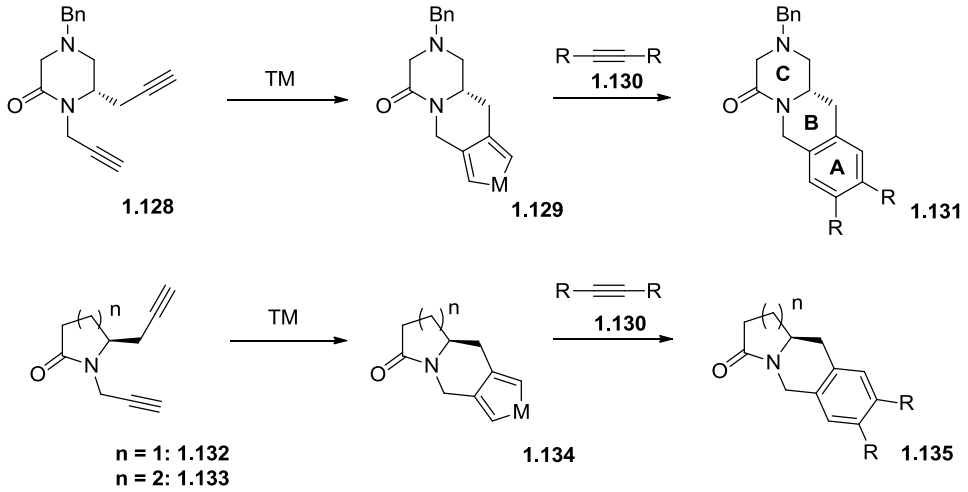
In order to prepare structurally diverse molecules it is envisaged that a late-stage transition metal mediated [2+2+2] cyclotrimerisation of alkynes could be used as a key component of the synthetic strategy. This would be contrary to the existing literature on THIQs anti-tumour antibiotics synthetic methodology

and would allow a unique opportunity for the introduction of various aromatic substituents useful for further chemical manipulation.

1.6 Aims and objectives

The main aim of this study is to apply transition-metal catalysed [2+2+2] cyclotrimerisation of alkynes to the synthesis of small molecules that resemble THIQs for biological investigation. In order to carry this out, three specific objectives will be pursued.

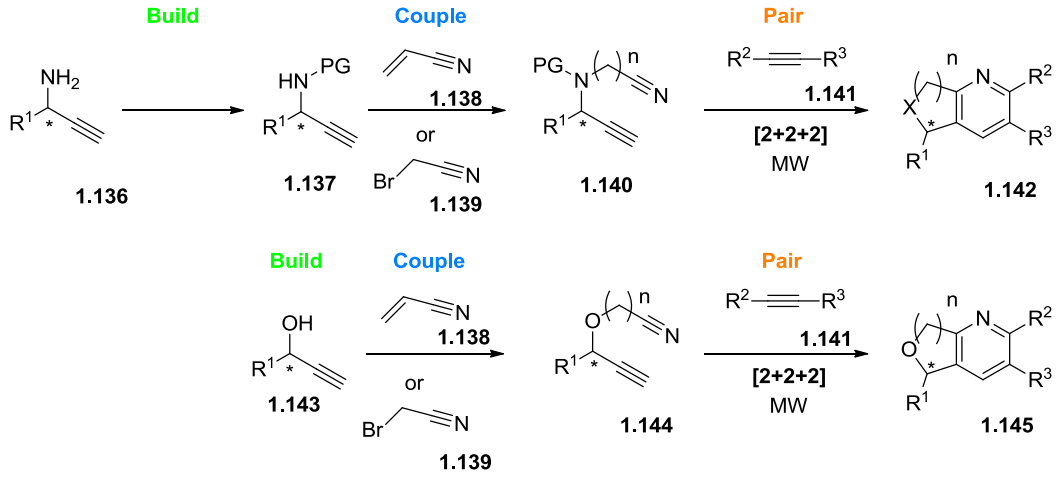
i. Design and synthesis of a tricyclic model system



Scheme 22

The objective is to develop a short and concise synthesis to the three tethered dialkyne intermediates **1.128**, **1.132** and **1.133** (Scheme 22) and then investigate different transition-metals for the [2+2+2] cyclotrimerisation of the tethered dialkynes with a small library of commercially available monoalkynes in order to generate the simple THIQ tricyclic compounds **1.131** and **1.135** (ring A and B) in one step.

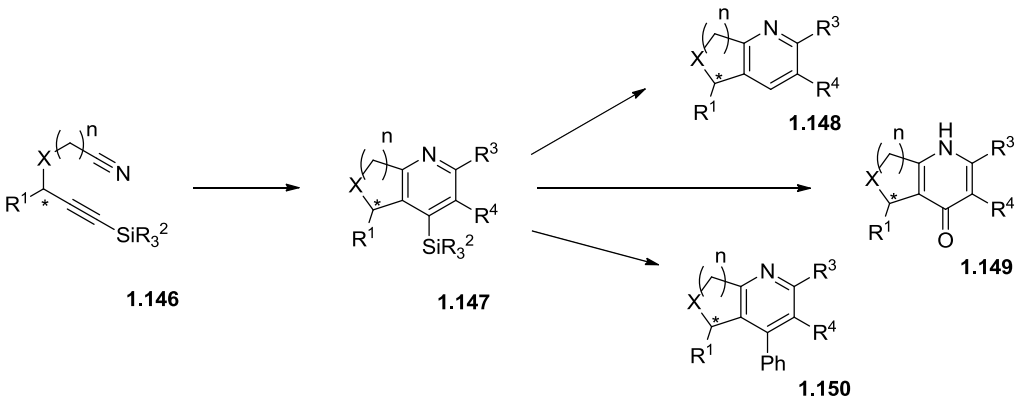
ii. Diversity-oriented synthesis using microwave assisted radiation



Scheme 23

The objective is to synthesise heterocyclic molecules by applying the concept of DOS and B/C/P in order to generate NCEs. The transition-metal catalysed [2+2+2] cyclotrimerisations will be performed using microwave assisted synthesis (Scheme 23).

As a starting point, racemic building blocks will be generated followed by optimisation of the methodology to enable the synthesis of both enantiomers. In order to increase diversity in the building block architecture, both oxygen (Scheme 23 bottom) and nitrogen (Scheme 23 top) atoms will be incorporated.



Scheme 24

To generate a broader library of compounds, the terminal alkyne will be silylated before pairing which will potentially allow further functionalisation after cyclotrimerisation by (i) removing the silyl group, (ii) oxidation to pyridone

derivatives and (iii) performing a cross coupling reaction to introduce a new chemical handle for enabling chemical diversity (Scheme 24).

iii. Biological evaluation of small molecules

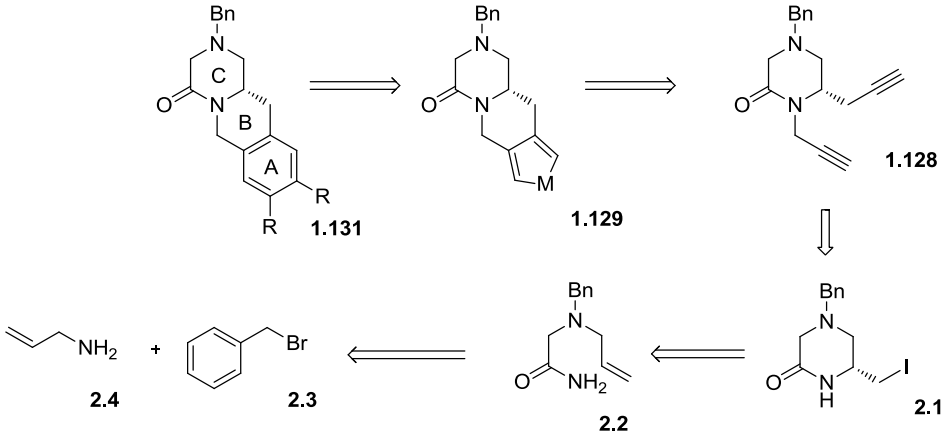
The objective is to biologically evaluate truncated THIQs and other related small molecules. In the first instance, new compounds will be assessed for the cytotoxic potential in cell lines known to be deficient or proficient in extra-hepatic CYP1A1, 1B1 and 2W1 enzymes. Selected molecules will also be assessed for their potential to inhibit the HIF-1 pathway and cell migration.

Chapter 2 Exploration of transition-metal catalysed [2+2+2] cyclotrimerisation of alkynes in the design and synthesis of tricyclic tetrahydroisoquinoline-based molecules

2.1 Synthesis of dialkynes

2.1.1 Towards the synthesis of (*S*)-4-benzyl-1,6-di(prop-2-yn-1-yl)piperazin-2-one

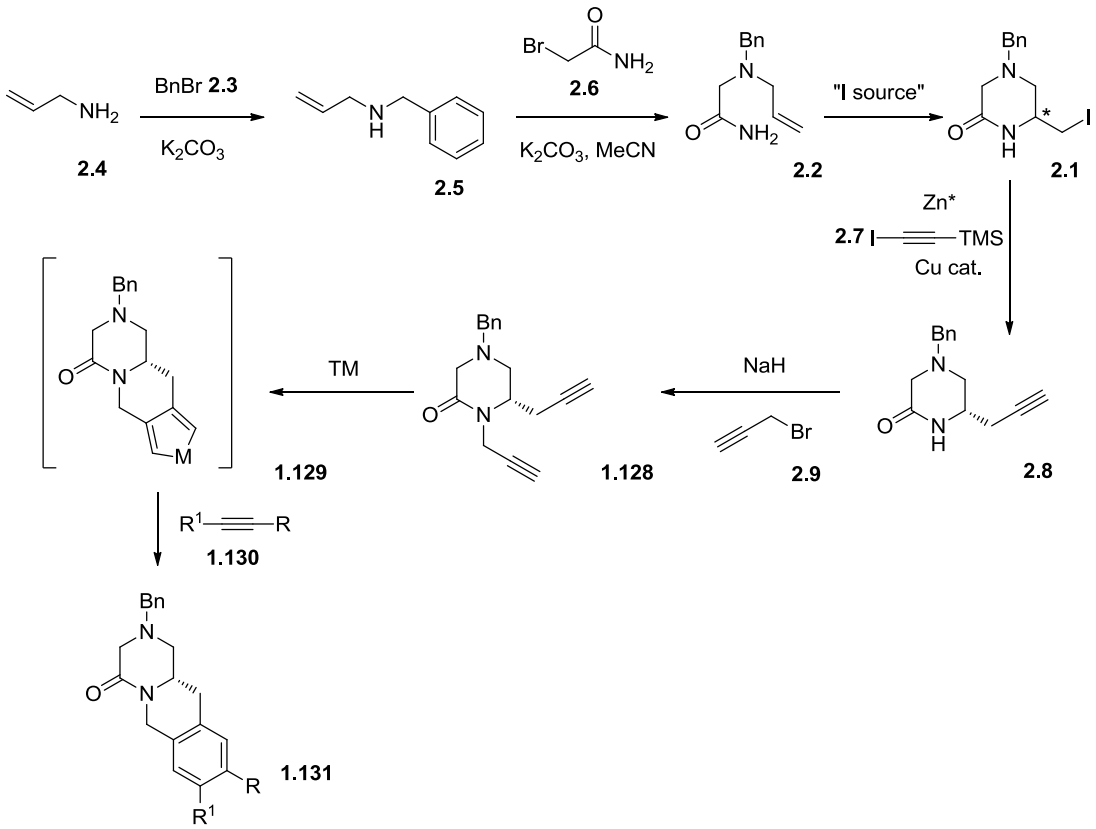
2.1.1.1 Retrosynthetic analysis



Scheme 25

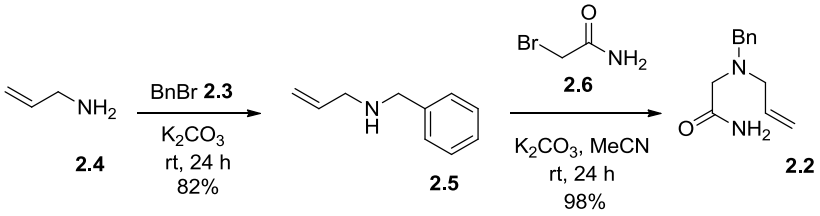
Retrosynthetically, the model system **1.131** (“ABC” skeleton) was envisaged to be constructed by cyclotrimerisation of dialkyne **1.128** and an acetylene derivative with a transition-metal catalyst, affording rings A and B in one step (Scheme 25). Dialkyne **1.128** was planned to be synthesised from iodolactam **2.1**, which in turn could be obtained from the readily available and inexpensive building blocks *N*-allylamine **2.4** and benzyl bromide **2.3**.

The initially proposed synthetic route is presented below (Scheme 26):



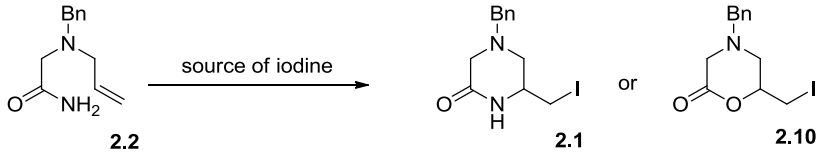
Scheme 26

2.1.1.2 Iodolactam formation via halocyclisation



Scheme 27

N-allylamine **2.4** was reacted with benzyl bromide **2.3** affording *N,N*-allylbenzylamine **2.5** in 82% yield (yield based on benzyl bromide **2.3**) (Scheme 27).[75] Treatment of **2.5** with 2-bromoacetamide **2.6** in acetonitrile afforded 2-(allyl(benzyl)amino)acetamide **2.2** in 98% yield.



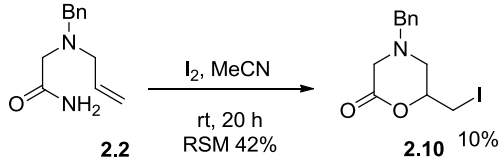
2.2 2.1 2.10

Scheme 28

Entry	Reagents	Solvents	Time (h)	Yield (%)		
				RSM 2.2	2.10	2.1
1	I_2	MeCN	20.5	42	10	---
2	NIS	Dioxane/MeOH Aq. NaOH	0.5	Degradation		
3	TMSOTf, NEt_3 then I_2	Hexane THF	1st step: 0.5 2nd step: 17.5	trace	---	25
4	TMSOTf, NEt_3 then I_2	Hexane THF	1st step: 0.5 2nd step: 2	---	18	---
5	TMSOTf, NEt_3 then I_2	Pentane THF	1st step: 3 2nd step: 2	37	5.4	30
6	TMSOTf, NEt_3 then I_2	DCM THF	1st step: 3 2nd step: 2	Did not react		
7	TMSOTf, NEt_3 then I_2	Et_2O	1st step: 3 2nd step: 2	Degradation		
8	TMSOTf, NEt_3 then I_2	Pentane THF (50 ºC)	1st step: 3 2nd step: 2	Degradation		
9	TMSOTf, NEt_3, DMAP then I_2	Pentane THF	1st step: 3 2nd step: 2	---	trace	---
10	TMSOTf, NEt_3, then I_2	Pentane MeCN (80 ºC)	1st step: 3 2nd step: 2	Degradation		
11	TMSOTf, NEt_3 then I_2	Pentane THF	1st step: 3 2nd step: 24	Degradation		
12	LDA, 0 ºC then I_2	THF	0.5 52	Did not react		
13	TMSOTf, NEt_3 $Br^+(collidine)_2PF_6^-$	Pentane DCM	1st step: 1 2nd step: 21	---	---	---
14	$I^+(collidine)_2PF_6^-$	DCM	2	Did not react		

Table II – Attempts to synthesise iodolactam 2.1.

The subsequent step was to ring close amide **2.2** *via* iodolactamisation to form the desired piperazine-2-one **2.1** (Scheme 28). Halocyclisations are more commonly described for lactones rather than lactams, because cyclisation of amides often produce lactones as well.[76,77,78] There are several methods described in the literature for iodolactamisations, for example the use of I_2/MeCN,[79] NIS,[80] *N,O*-bis-silylation[81]. The use of LiOH, ^{n}BuLi and LiAl(O^{t}Bu)$_4$ as the base has also been successfully applied in iodolactamisation reactions.[82,83]



Scheme 29

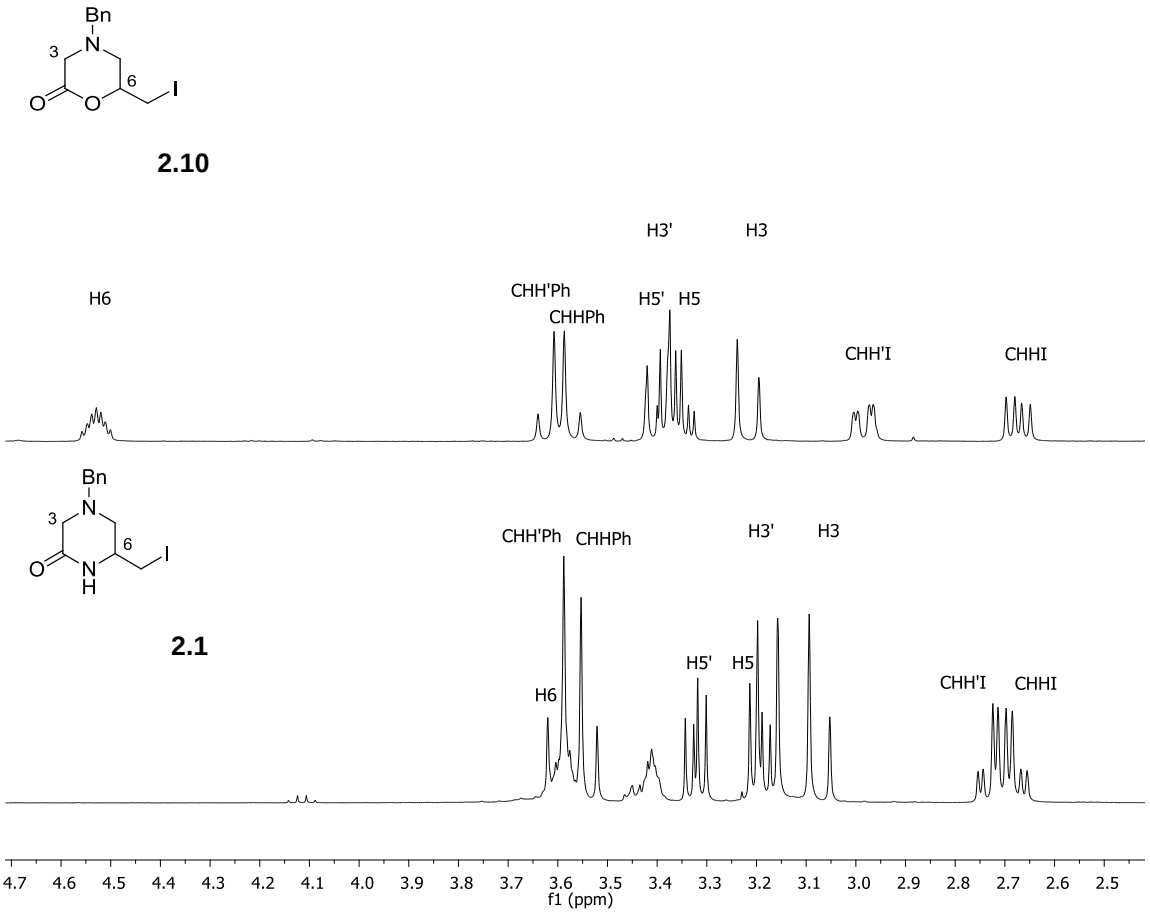
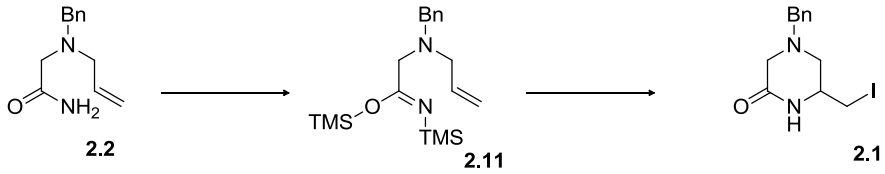


Figure 10 – ^{1}H NMR of lactone 2.10 (top) and lactam 2.1 (bottom).

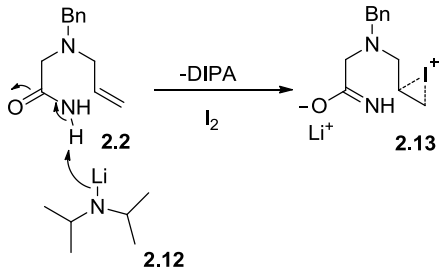
In the first attempt, I_2 (4 eq.) in acetonitrile (MeCN) was used as this is the most straightforward method of iodocyclisation.[79] After 20 h, 42% of starting material **2.2** was recovered and 10% of a new compound was obtained (Table II, entry 1). NMR and mass analysis revealed that this compound was lactone **2.10** instead of lactam **2.1** (Scheme 29). ^{1}H NMR analysis (Figure 10 top) showed that the terminal alkene signal at 5.20 and 5.24 ppm (CHH') had disappeared, so the double bond had reacted. In the product a new signal appeared at 4.46 ppm (δ_H) and 77.8 ppm (δ_C) consistent with H-6 being α to an oxygen rather than a nitrogen atom. The iodo-cyclisation was further confirmed by the appearance of the CH_2I signal at lower chemical shifts, characteristic of a methylene group α to iodine (δ_C = 3.6 ppm).



Scheme 30

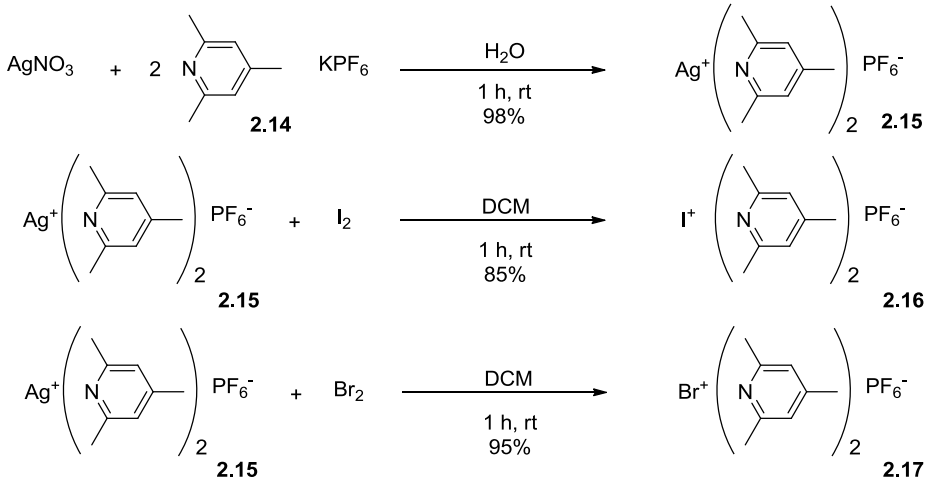
As a consequence, it was decided to follow a method reported by Knapp which uses trimethylsilyl trifluoromethanesulfonate (TMSOTf) and NEt_3 to form the bis-silylated intermediate **2.11**. Such bis-silylated intermediates have been shown to react with iodine to obtain the desired product (Scheme 30).[81] In the first attempt (entry 3) amide **2.2** was reacted with TMSOTf affording 25% yield of lactam **2.1** and trace quantities of starting material. With this encouraging result, the next step was to try to find better conditions to enhance the yield of lactam **2.1**. Different reaction times (30 minutes and 3 h) and different solvents (hexane, pentane, dichloromethane (DCM), Et_2O) were tried for the 1st step (entry 3, 5 6 and 7, respectively, Table II). Use of 4-dimethylaminopyridine (DMAP) in the silylation step has been reported by Moody,[84] but did not promote lactam formation in this attempt (entry 9). Since the formation of 6-membered rings is often slower than with 5-membered rings because of the greater entropy of activation, the iodocyclisation step was carried out at higher temperatures. After addition of iodine, the reaction mixture was heated in tetrahydrofuran (THF) at 50 ºC or in MeCN at 80 ºC (entries 8 and 10), however the elevated temperatures led to decomposition of the reaction mixture. The

best result was obtained when the bis-silylation was carried out in pentane over 3 h and the iodocyclisation was carried out in THF during 2 h (entry 5). Using these conditions lactam **2.1** (30%) and lactone **2.10** (5.4%) were obtained as products, but 37% of starting material **2.2** was also recovered.



Scheme 31

Since this approach proved to be capricious, other cyclisation methods were investigated. In a first approach lithium diisopropylamine (LDA) was used to generate the amide anion of **2.2**, followed by addition of I_2 (Scheme 31). No reaction occurred after an extended reaction time (52 h) (entry 12).

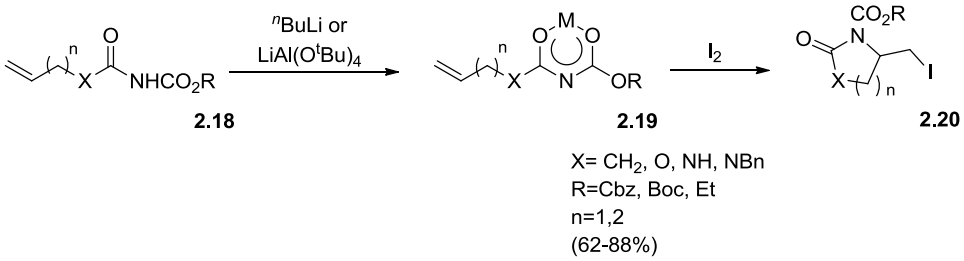


Scheme 32

Knapp has also investigated the use of iodonium *bis*(collidine) hexafluorophosphate **2.16** as a source of iodine for the cyclisation step.[81] With that in mind, iodonium *bis*(collidine)iodine hexafluorophosphate **2.16** and bromonium *bis*(collidine)iodine hexafluorophosphate **2.17** were synthesised from the reaction of silver nitrate, collidine **2.14** and potassium

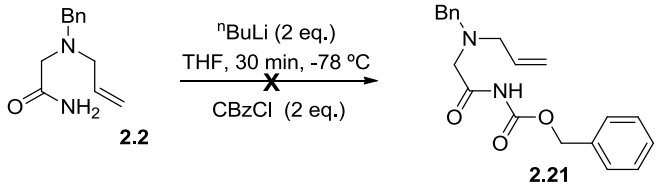
hexafluorophosphate (Scheme 32), followed by halogenation of the resulting silver salt **2.15**.[85]

Using Knapp's protocol,[86] the bis-silylation step was performed with TMSOTf and NEt_3 in pentane (entry 13) and bromonium *bis*(collidine) hexafluorophosphate **2.17** in DCM was used as the electrophile in the cyclisation step. The resulting mixture was stirred for 21 h and the reaction was stopped after all starting material had been consumed (Table II, entry 13). After purification, the compounds isolated weremixtures and none matched the desired product. Iodination with iodonium *bis*(collidine) hexafluorophosphate **2.16** in DCM was also investigated, based on the use of this salt for the preparation of medium-ring lactones and lactams (entry 14).[77] After 3 h, the reaction was stopped because the starting material was no longer visible by tlc, however after an aqueous work up, only starting material was recovered, indicating that an intermediate had been formed, but was unstable to the extraction conditions leading to reversal of the reaction.



Scheme 33

Literature reports on the formation of 6-membered ring iodolactams in good yields from cyclisation of the lithium salt derived from an amide-carbamate with an iodine source (Scheme 33).[83]

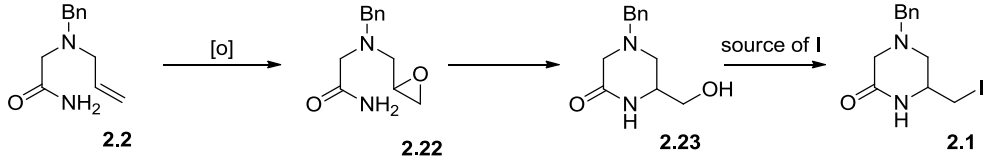


Scheme 34

Entry	Reagents	Conditions	Time/h	Observations
1	1.BuLi (2 eq.) 2.CBzCl(1.2 eq.)	THF (-78 ºC)	0.5 1.5	Degradation
2	Ethyl chloroformate (2 eq.), NEt_3 (1.3 eq.)	THF	24	Did not react
3	1. $(COCl)_2$ (1.2 eq.) 2. ^{t}BuOH (2.1 eq.)	1,2-DCE, reflux 0 ºC	2.5 1.5	Degradation
4	1. $(COCl)_2$ (1.2 eq.) DMAP (0.2 eq.), NEt_3 (2 eq.) 2. ^{t}BuOH (2.1 eq.)	1,2-DCE, reflux 0 ºC	5 17.5	Did not react
5	$(Boc)_2O$ (1.5 eq.), DMAP (0.2 eq.), NEt_3 (2 eq.)	1,2-DCE, reflux	24	Did not react

Table III – Attempts to protect the amide group of compound 2.2.

Consequently, it was decided to protect amide **2.2** with benzyl chloroformate (CBzCl) (Scheme 34), prior to cyclisation with the reported methods. The protection was attempted using ^{n}BuLi in THF and CBzCl at -78 ºC (Table III, entry 1).[87] After 1.5 h the starting material was consumed but the reaction mixture degraded. Deducing that the use of a strong base led to decomposition of the starting material, NEt_3 was employed as the base in a reaction with ethyl chloroformate (entry 2)[88,89] but no reaction was observed. In the last attempt the amide **2.2** was Boc protected[90,91,92] using oxalyl chloride/^{t}BuOH or Boc_2O (entries 3-5), however these attempts were also unsuccessful.



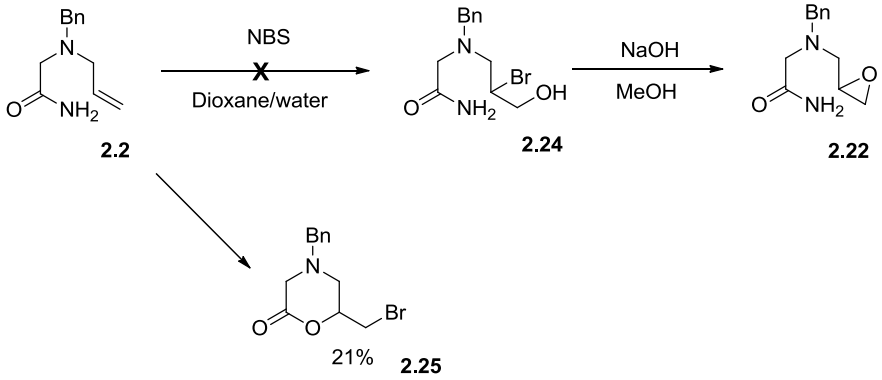
2.2 **2.22** **2.23** **2.1**

Scheme 35

Entry	Reagents	Solvent	Time/h	Observations
1	*m*-CPBA (1.2 eq.), -20 ºC-rt	DCM	5	Did not react
2	*m*-CPBA (1.1 eq.), reflux	DCM	1	*N*-oxide
3	1. $BF_3.Et_2O$ (1.5 eq.), -78 ºC 2. DMDO (2 eq.)	THF	2 2	Did not react
4	1. TCA (5 eq.) 2. *m*-CPBA (1.1 eq.)	DCM	0.08 24	Did not react

Table IV – Attempts to epoxidise compound 2.2.

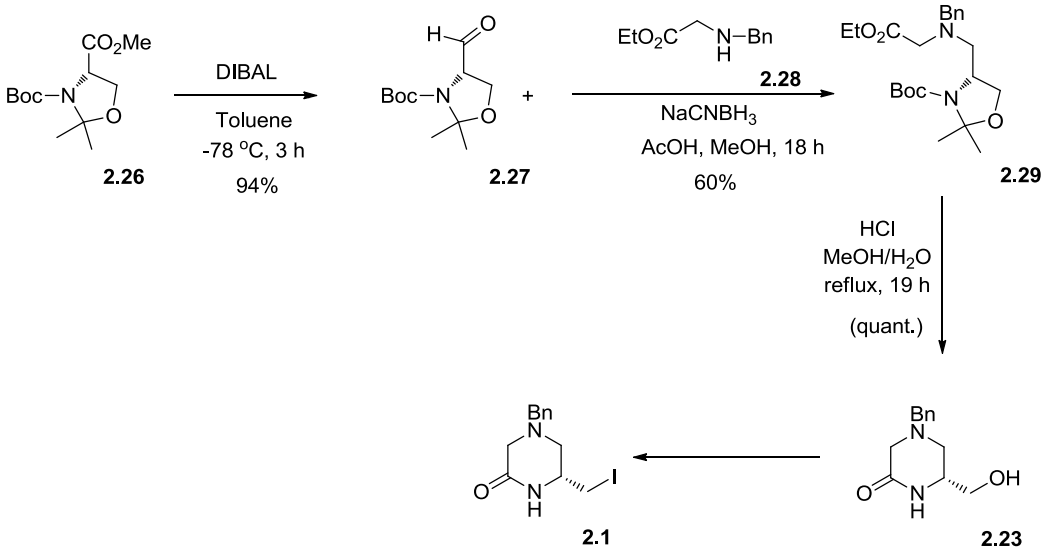
Another strategy attempted involved generation of an epoxide from amide **2.2**, followed by ring closure and conversion of the alcohol **2.23** into the corresponding iodide **2.1** (Scheme 35). When *meta*-chloroperoxybenzoic acid (*m*-CPBA)[93] was used for the epoxidation at rt (Table IV, entry 1) the reaction was not complete after 5 h. Increasing the reaction temperature to reflux (entry 2) led to the consumption of all the SM and formation of a very polar compound which was believed to be the *N*-oxide formed by the oxidation of the tertiary amine (^{1}H NMR showed that the alkene had not reacted). Epoxidation of compound **2.2** using dimethyldioxirane (DMDO)[94] in the presence of $BF_3{\cdot}OEt_2$ was also attempted (entry 3).[95] It was believed that the non-protic Lewis acid would form an adduct with the tertiary amine, protecting it from *N*-oxidation during epoxidation of the alkene. Trichloroacetic acid (TCA) was also employed towards the same outcome (entry 4)[96] however in both reactions the starting material did not react.



Scheme 36

An alternative route to the epoxide employs *N*-bromosuccinimide (NBS) for bromohydroxylation of the double bond followed by epoxide ring closure[97] (Scheme 36). Despite the use of H_2O in the solvent system the bromohydrin **2.24** was not obtained; instead lactone **2.25** (21% yield) was isolated.

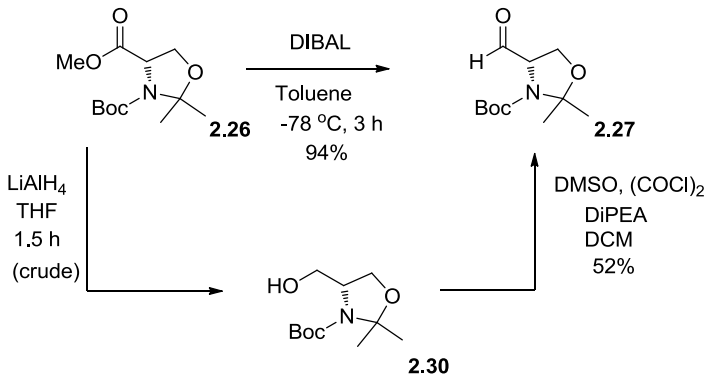
2.1.1.3 Iodolactam formation via Garner's aldehyde



Scheme 37

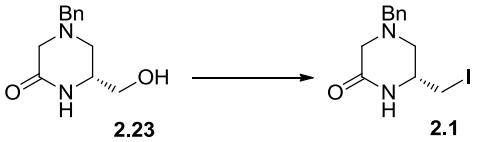
Since all attempts at forming the lactam via halocyclisation had proven unsuccessful, another strategy was developed in order to produce lactam **2.1**. Garner's aldehyde[98] **2.27** was subjected to a reductive amination, followed by a cyclisation to produce alcohol **2.23**, which could then be transformed into the corresponding iodolactam **2.1**, (Scheme 37).

Garner's aldehyde **2.27** was obtained in good yield by reduction of the commercially available ester **2.26** with diisobutylaluminium hydride (DIBAL) in toluene. Reductive amination of aldehyde **2.27** with *N*-benzylglycine ethyl ester **2.28** and sodium cyanoborohydride afforded amine **2.29** in a moderate yield (60%). Deprotection of the isopropylidene and Boc groups under acidic conditions followed by cyclisation generated hydroxylactam **2.23** in quantitative yield and high purity.[98]



Scheme 38

An alternative approach to Garner's aldehyde **2.27** involved reduction of the commercial ester **2.26** using $LiAlH_4$ (Scheme 38) to the corresponding alcohol **2.30** followed by Swern oxidation.[99] Garner's aldehyde **2.27** was obtained in 52% yield, making this route less viable.



2.23 **2.1**

Scheme 39

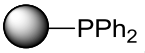
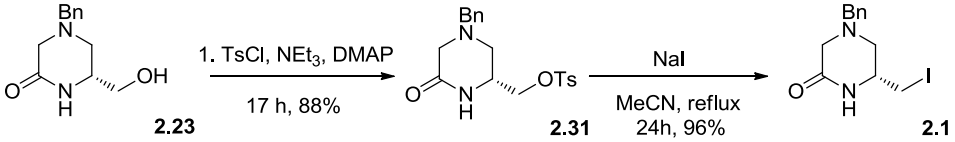
Entry	Reagents	Solvents	Temperature (ºC)	Time/h	Yield (%)
1	PPh_3, Im, I_2	Benzene/MeCN	rt	3	✓[a]
2	CDP, Im, I_2	PhMe, MeCN	rt	0.5	---
3	$Me^+P(PhOMe)_3I^-$	THF	rt	2	47
4	 PPh_2, Im, I_2	Toluene	50	5	86

Table V – Attempts to convert alcohol 2.23 into lactam 2.1. [a] Product difficult to separate from PPh_3O

Conversion of alcohol **2.23** to iodide **2.1** (Scheme 39) was first attempted using PPh_3, I_2 and imidazole (Table V, entry 1),[100] but the desired product proved difficult to separate from the triphenylphosphine oxide generated in the reaction mixture. Chlorodiphenylphosphine (CDP)/imidazole/I_2,[101] methyl triphenoxy phosphonium iodide[100] and a polymer-bound triphenylphosphine[101,102] were used to perform the direct conversion of alcohols into alkyl iodides without the purification issues arising from triphenylphosphine oxide as a side product. The best result was achieved when a triphenylphosphine polymer support was used (entry 4); iodolactam **2.1** was obtained with a yield of 86%.

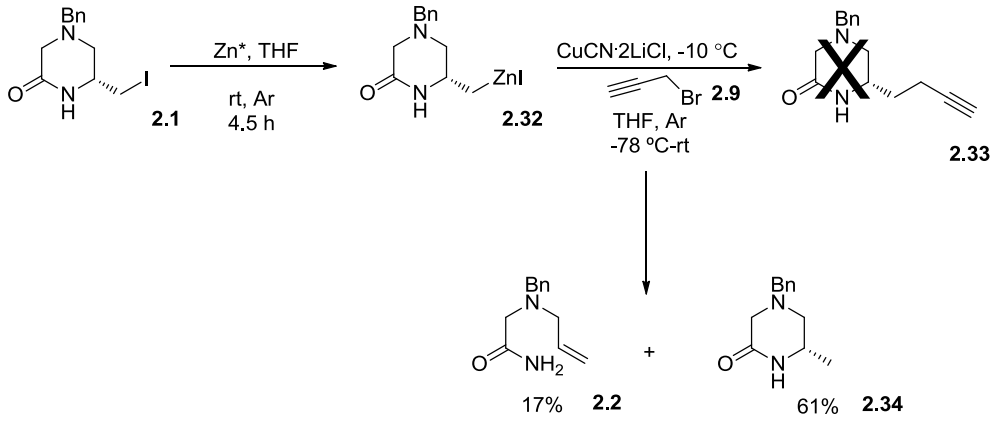


2.23 **2.31** **2.1**

Scheme 40

Finally, a Finkelstein reaction was investigated for the synthesis of iodolactam **2.1** (Scheme 40),[103] affording the desired compound **2.1** in 96% yield. Comparing the Finkelstein reaction with the use of polymer-bound

triphenylphosphine, both provide similar yields, however the product is quickly obtained using polymer supported triphenylphosphine and the oxidised polymer is easily removed by filtration. The disadvantage with the latter approach is that the polymer is quite expensive and therefore not ideal for scale-up reactions.

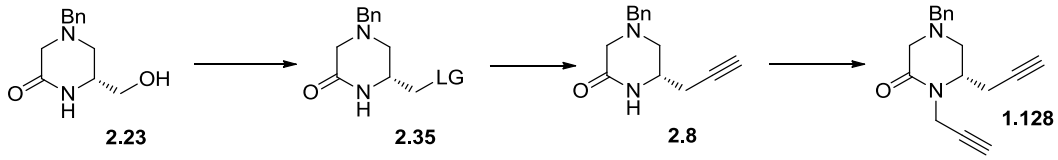


Scheme 41

With iodolactam **2.1** in hand, the next step was formation and coupling of the corresponding organozinc reagent. Alkylation of the organozinc with propargyl bromide was used as a model reaction to test the organozinc formation, prior to investigating its cross-coupling with alkenyliodides. A copper-mediated nucleophilic substitution of the organozinc **2.32** with propargyl bromide **2.9** was carried out. Insertion of activated zinc (Zn*) into the C-I bond in **2.1**, followed by transmetallation to copper (CuCN·2LiCl as the copper source) in THF, gives the organocuprate reagent, that should react with alkyne **2.9** to give **2.33** (Scheme 41).[103,104,105,106] The product distribution from the model reaction with propargyl bromide indicated that zinc was inserted (Scheme 41), however after addition of propargyl bromide **2.9** the desired product was not obtained. Instead, two other compounds were obtained, the unsaturated amine **2.2** (17%) which resulted from β-elimination (a known side product described for this type of reactions)[103] and methyl lactam **2.34** (61%). This reduced species may be formed as a result of self-quenching of lactam **2.32**, i.e. slow deprotonation of the amide functionality of **2.32** and/or related copper compound which yields **2.34** after work up. The same reaction was repeated with (iodoethynyl)trimethylsilane affording the same results in a similar yield, suggesting it is not a problem of alkyne reactivity but a problem in the transmetallation step. Therefore, a Negishi cross coupling reaction was attempted using $Pd_2(dba)_3$ as catalyst, Sphos as

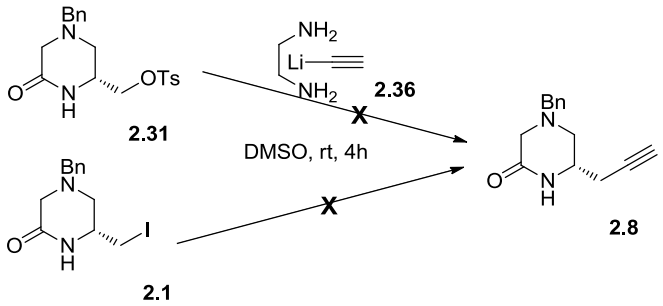
ligand (1:2 molar ratio), (iodoethynyl)trimethylsilane and DMF as solvent.[107] Unfortunately, no product was formed and no starting material was recovered, indicating degradation of the reaction mixture.

2.1.1.4 Towards alkyne synthesis by nucleophilic substitution



Scheme 42

The cross couplings described in the section above are air sensitive and are often described as providing low yields. Consequently it was decided to go back to alcohol **2.23** to see if it was possible to convert the alcohol into alkyne **2.8**, via displacement of a leaving group (Scheme 42).



Scheme 43

Given the lack of steric hindrance of the leaving group (LG) (Figure 11), both tosylate **2.31** and iodide **2.1** should be easily displaced by lithium acetylide-ethylenediamine complex **2.36** (LAED) to afford the desired alkyne **2.8** (approach of the nucleophile indicated with a green arrow). However no desired product could be isolated from either reaction due to degradation of the reaction mixture (Scheme 43).

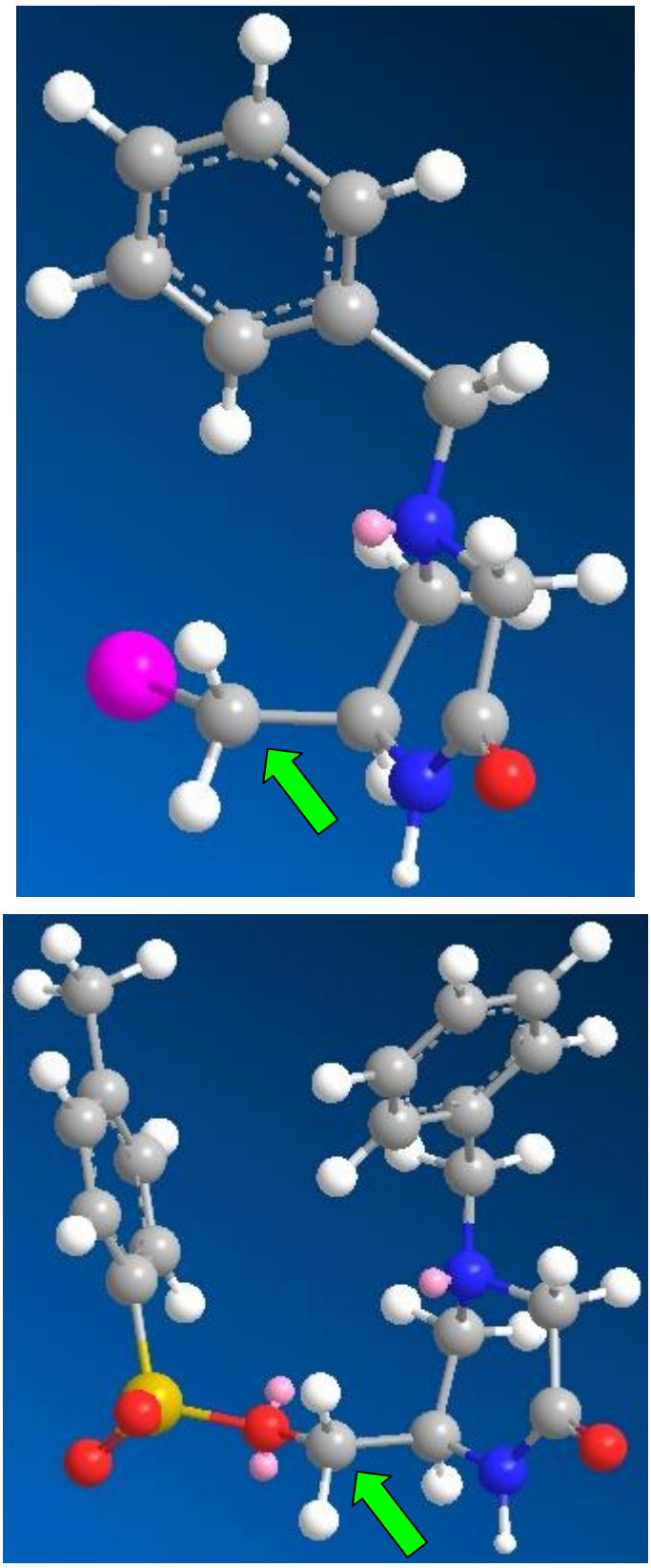
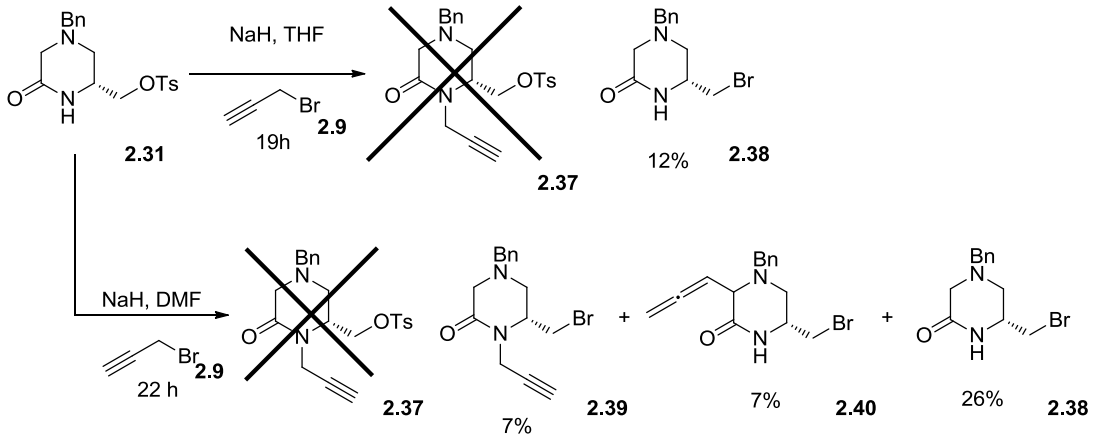
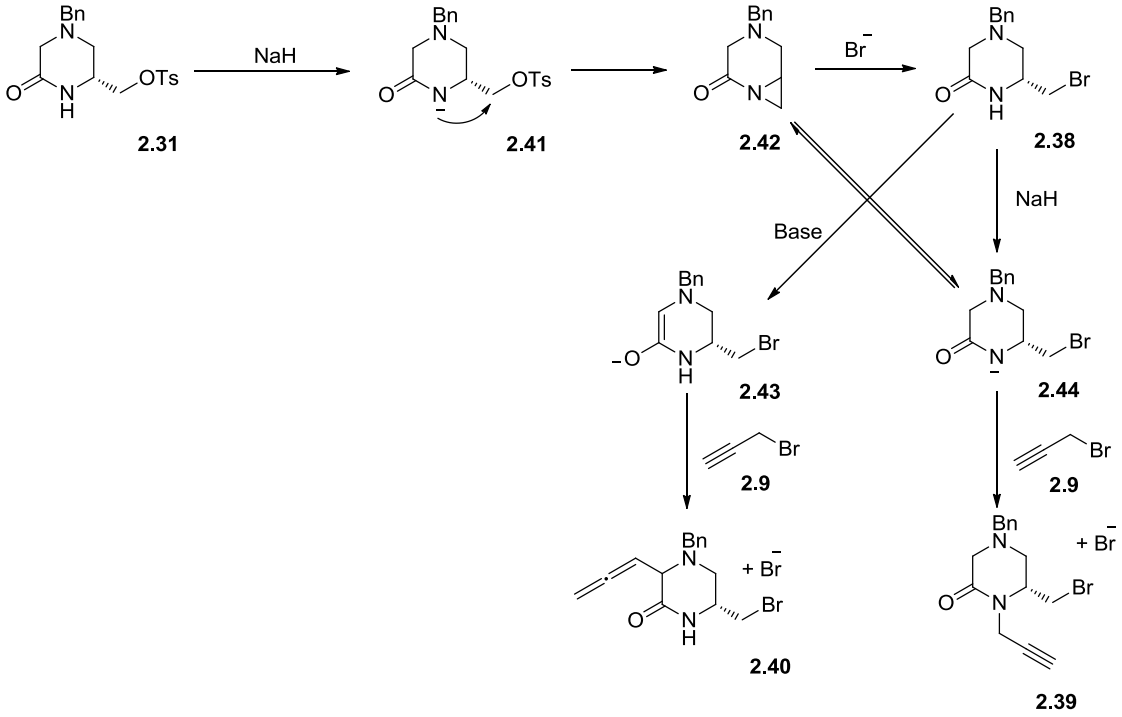


Figure 11 – Minimised energy conformations in vacuum for compounds 2.1 (top) and 2.31 (bottom). * Structures modeled using *ChemBio3D* and minimised to give the lower energy state.

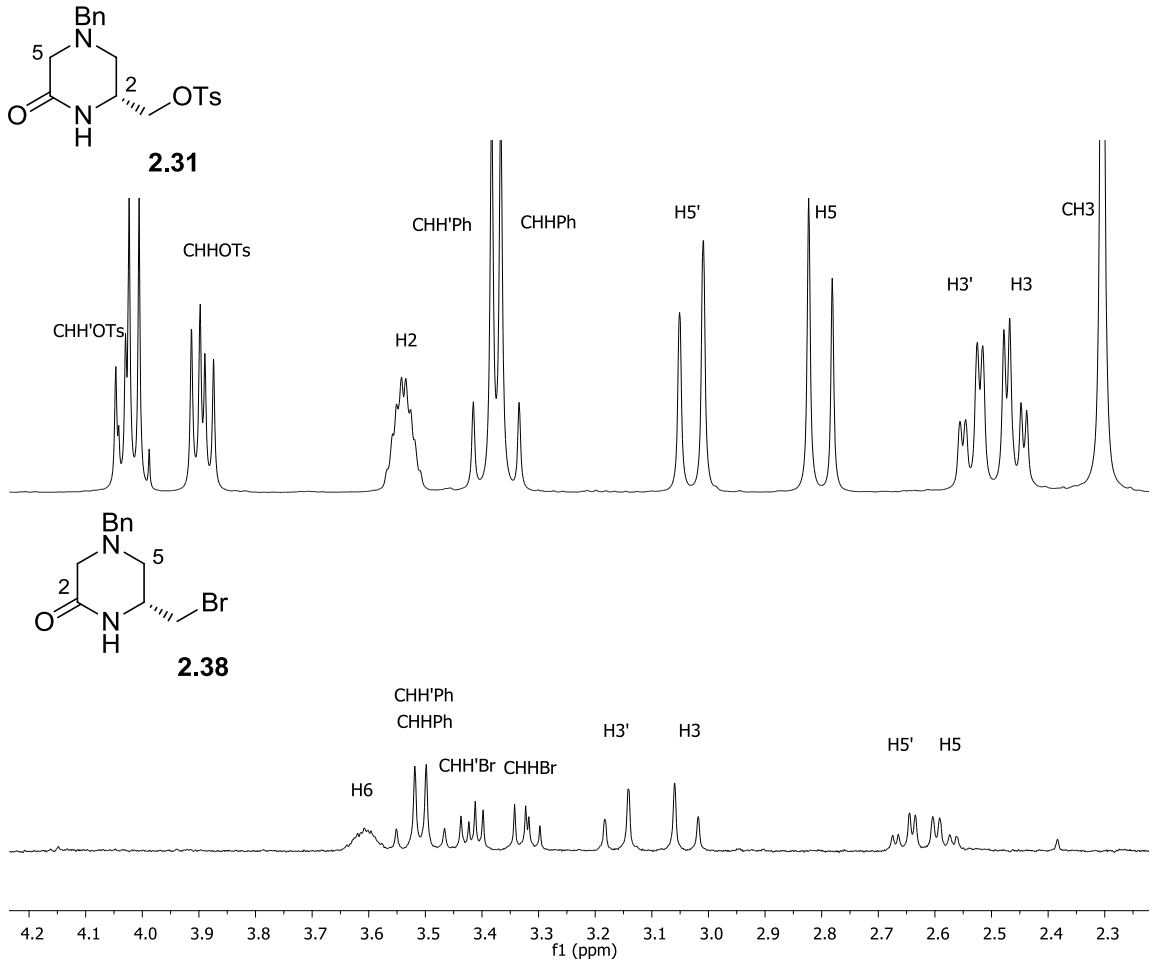


Scheme 44

The failure of the tosylate displacement may also have been due to deprotonation of the amide proton by lithium acetylide, so it was decided to block this position by reaction with propargyl bromide **2.9** (Scheme 44). Unfortunately, the desired propargylation was not achieved. Instead three new compounds were obtained, bromolactam **2.38**, bromoalkyne **2.39** and bromoallene **2.40**. Their formation can be explained by the mechanism shown below (Scheme 45).



Scheme 45



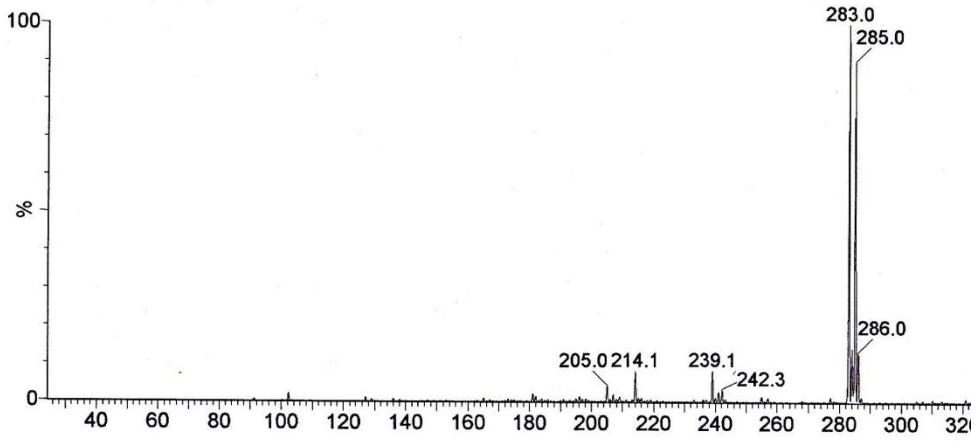


Figure 12 – ^{1}H NMR of tosylate 2.31 (top) and bromolactam 2.38 (bottom) and mass spectrum of 2.38.

As per normal procedure, these structures were assigned by NMR spectroscopy as well as mass spectrometry. A change in chemical shift of the sidechain methylene protons to ~3.5 ppm is consitent with formation of bromolactam **2.38**, which is more shielded than in the starting material (~4 ppm)

(Figure 12). Mass spectrometry shows a molecular ion characteristic of bromine-containing compounds (m/z (ESI+) 283 (100% $C_{12}H_{15}{}^{79}BrN_2O$), 285 (98% $C_{12}H_{15}{}^{81}BrN_2O$) $[M]^+$) since the two bromine isotopes have a natural abundance of 100:98.

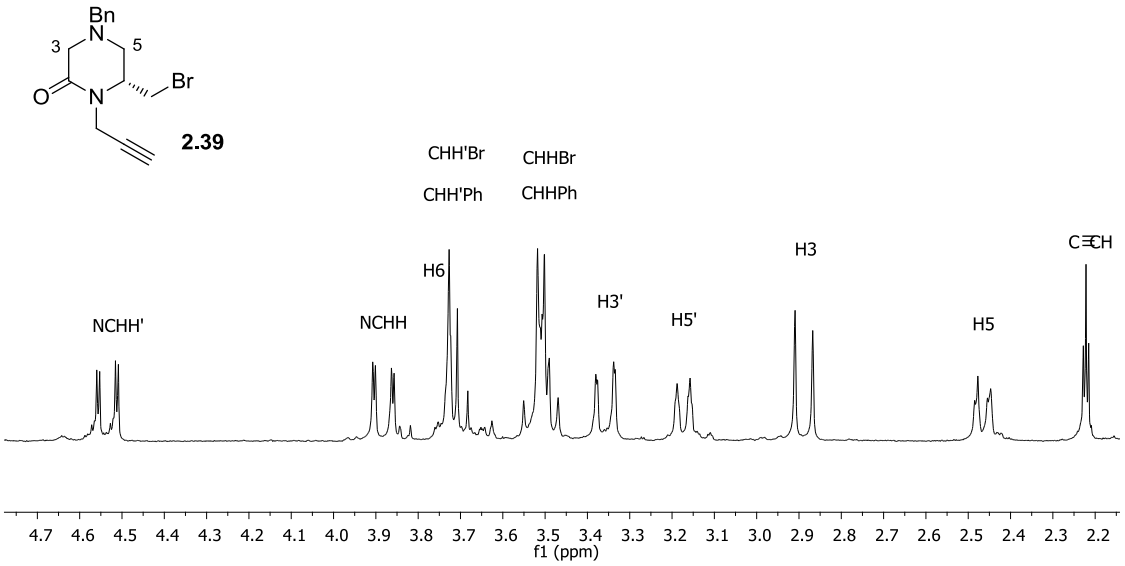


Figure 13 – ^{1}H NMR of bromoalkyne 2.39.

Compound **2.39** differs from compound **2.38** due to the presence of the alkyne moiety. The ^{1}H NMR shows the appearance of a triplet (2.22 ppm, C≡CH), characteristic of terminal alkynes, as well as two double doublets further downfield (3.88 and 4.53 ppm) which correspond to NCHH and NCHH' (Figure 13). The presence of the alkyne was also confirmed by ^{13}C and DEPT NMR. The quaternary carbon from the triple bond appears at 73.2 ppm as expected for alkynes and the terminal carbon appears at 78.0 ppm. Mass spectrometry also revealed a characteristic isotope pattern indicating that bromination had taken place.

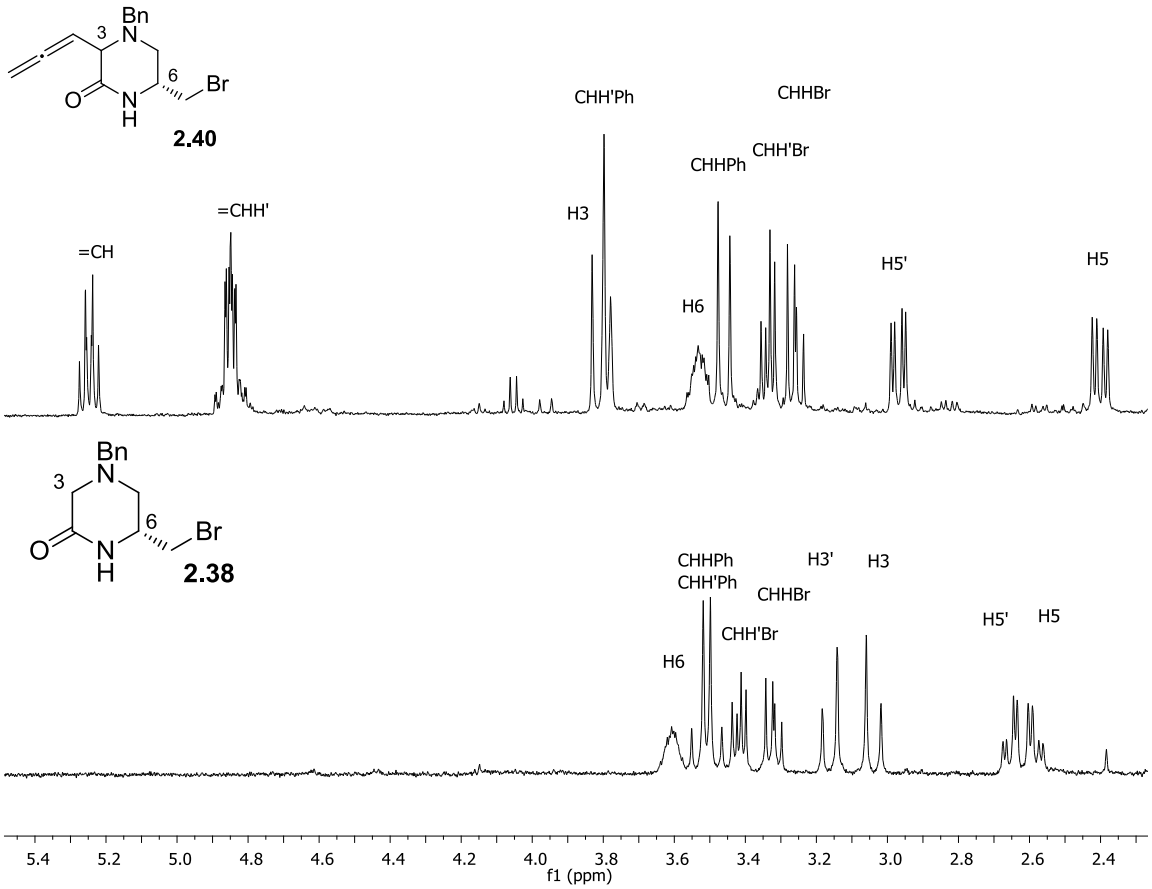


Figure 14 – ^{1}H NMR of bromoallene 2.40 (top) and bromolactam 2.38 (bottom).

Finally, when comparing bromolactam **2.38** with allene **2.40** it can be seen that one of the H3 proton signals had disappeared and there are two new signals, a multiplet at 4.90-4.80 ppm (2H) corresponding to =CHH' and a double triplet (1H) corresponding to =CH (Figure 14 top). The coupling between H3 and =CH can be seen in the COSY spectrum (Figure 15 top) and the correlation between allene carbon and =CHH' and H3 can be seen in the HMBC spectrum. ^{13}C reveals the presence of the quaternary allene carbon at 210.5 ppm (Figure 15 bottom).

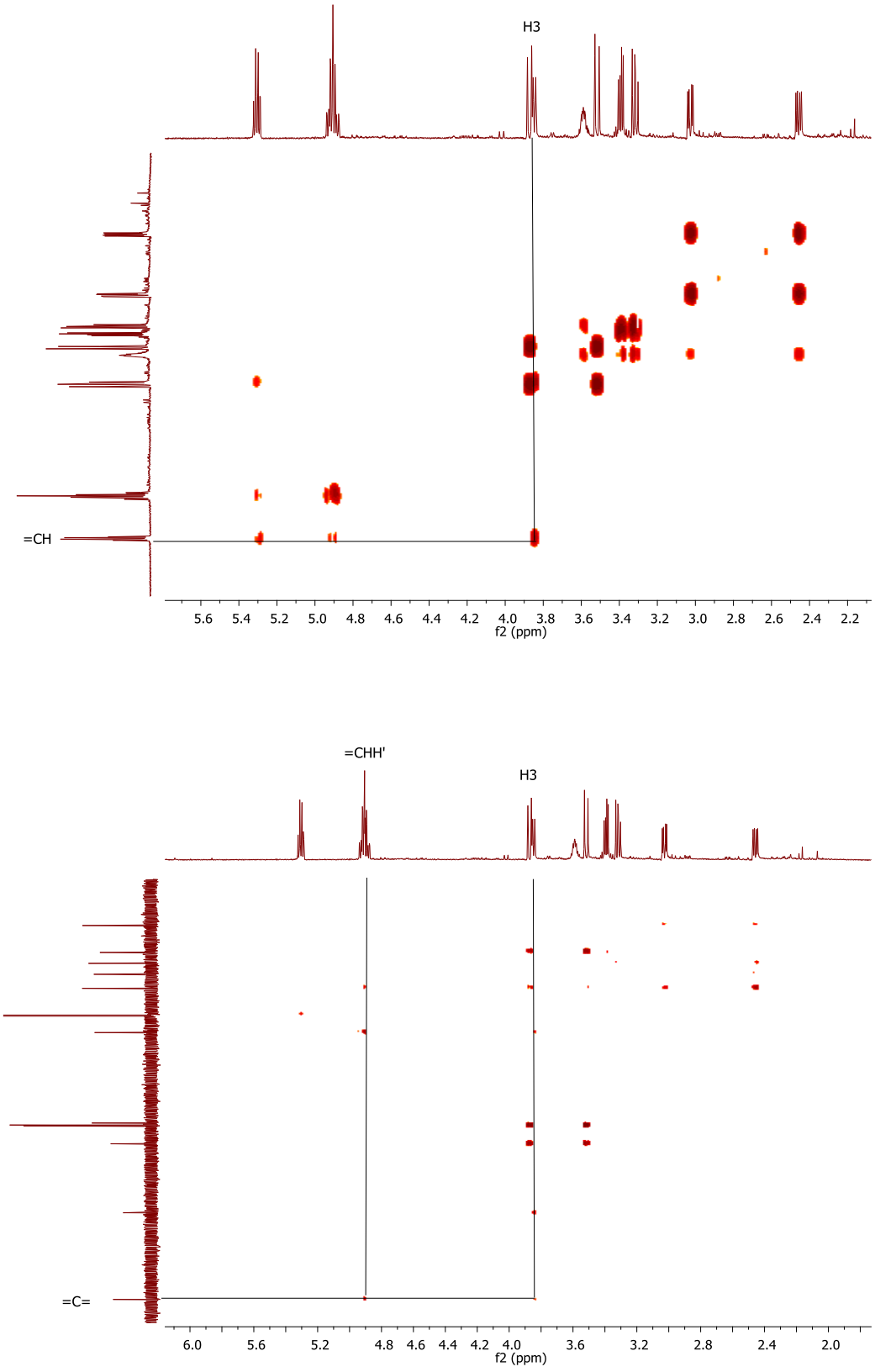
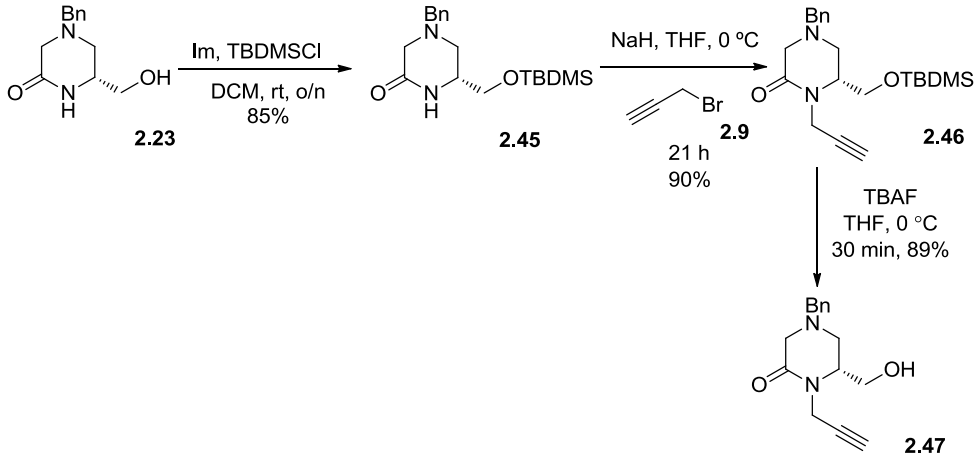


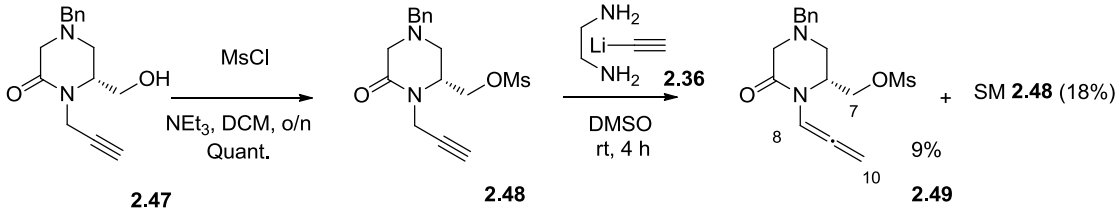
Figure 15 – COSY (top) and HMBC (bottom) spectra of allene 2.40.

2.1.1.5 Towards dialkyne synthesis by alkylation of lactam



Scheme 46

The results obtained above suggest that the amide NH needed to be functionalised prior to activation of the hydroxyl group. Alcohol **2.23** was protected with *t*-butyldimethysilylchloride (TBDMSCl) and the crude product **2.45** propargylated with NaH and propargyl bromide **2.9** in THF affording alkyne **2.46** in 90% yield (Scheme 46).[108] Deprotection of alkyne **2.46** was successfully achieved using tetrabutylammonium fluoride (TBAF) yielding alcohol **2.47** in near quantitative yield without any need for further purification.[109]



Scheme 47

To insert the second alkyne, it was planned to convert alcohol **2.47** into a good leaving group, as previously shown (section 2.1.1.3), and then react it with LAED **2.36**. This time a mesylate was chosen to see if this leaving group would afford different results to those obtained when tosylate **2.31** and iodide **2.1** were used (Scheme 43). Thus, alkyne **2.47** was reacted with mesyl chloride and NEt_3 in DCM and the resulting product **2.48** was used in the next step without further purification (Scheme 47).[110] Reaction of mesylate **2.48** with LAED **2.36** as previously described, yielded allene **2.49** rather than the desired dialkyne **1.128**.

Tosylate was also employed as a leaving group, but the reaction mixture degraded. Based on these observations, triflate was chosen as a better leaving group. Reaction of alcohol **2.47** with triflic anhydride, 2,6-lutidine in DCM, at -78 ºC during 30 min led to reaction mixture decomposition.[111] Pyridine was also employed as a base instead of lutidine, but again the reaction mixture decomposed. Therefore, it was not possible to synthesise the triflate derivative.

2.1.2 Towards the synthesis of 1,5-di(prop-2-yn-1-yl)pyrrolidin-2-one

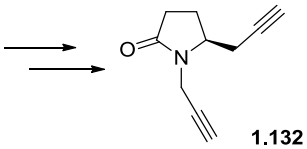
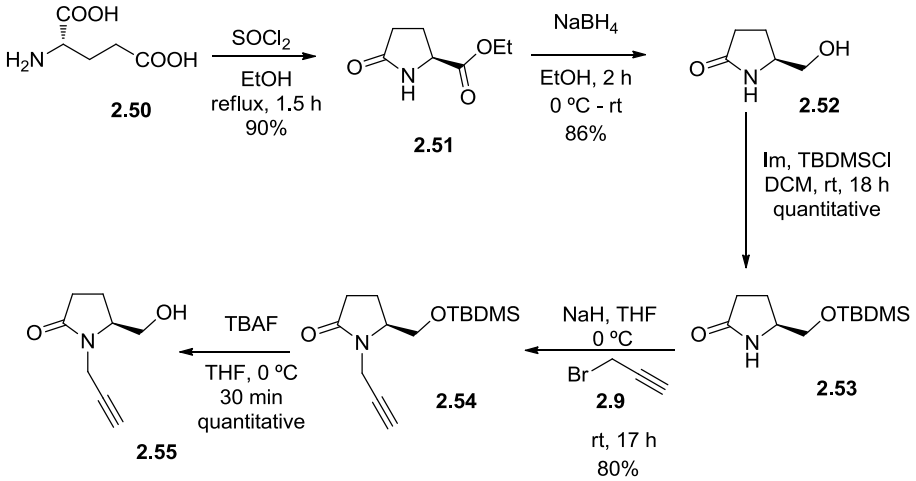


Figure 16 – Towards the synthesis of 1.132.

The synthetic obstacles in forming the dialkyne intermediate **1.128** prompted the investigation of a simplified five-membered ring system **1.132**, without a tertiary amine (Figure 16).

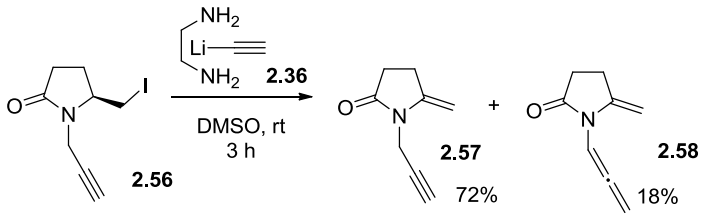
2.1.2.1 Towards dialkyne synthesis by initial nitrogen alkylation



Scheme 48

The first route investigated was based on that used to prepare the 6-membered ring system: functionalisation of the lactam, conversion of the alcohol into a leaving group and displacement of the leaving group by an alkyne nucleophile.

Ethyl-2-pyrrolidinone-5(*S*)-carboxylate **2.51** was obtained from the acid-catalysed cyclisation of commercially available L-glutamic acid **2.50** in 90% yield (Scheme 48).[112] Reduction of ester **2.51** with sodium borohydride generated alcohol **2.52** in very good yield. Subsequent protection of the alcohol **2.52** with TBDMSCl, propargylation of the amide *N*-H with propargyl bromide **2.9** and deprotection of the alcohol **2.54** with TBAF afforded alcohol **2.55** in quantitative yield.



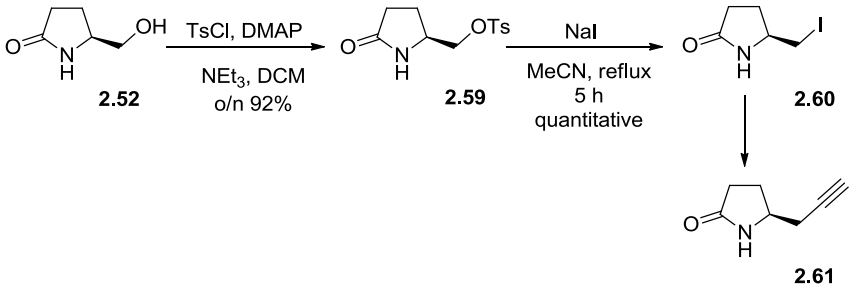
Scheme 49

With alkyne **2.55** in hand, the alcohol group was converted into three different leaving groups: mesylate, tosylate and iodine using the same conditions as used for the 6-membered ring. Each resulting compound was reacted with LAED **2.36**. The mesylate and tosylate derivatives decomposed when treated with LAED in DMSO, THF or hexamethylphosphoramide (HMPA), revealing that the solvent does not play an important role in the course of the reaction. Iodide **2.56** did not degrade, instead alkenes **2.57** and **2.58** were obtained (Scheme 49).

It is likely that the acidic H5 was abstracted by the lithium complex that acted as a base instead of acting as a nucleophile, subsequently expelling iodine to create the exocyclic alkene. The allene was also formed as a result of isomerisation of the triple bond in basic media.

The results with iodide **2.56** suggested that a change in the solvent system may modulate the reactivity of LAED **2.36**. Only starting material **2.56** was recovered when THF was used as the solvent. The reaction was also attempted with sodium acetylide in THF and HMPA,[113] and after 24 h only starting material was recovered indicating that the use of another nucleophile did not change the reactivity of the starting material.

2.1.2.2 Initial alkyne insertion *via* SN_2 or cross coupling at the alcohol



Scheme 50

Entry	Cross coupling reaction		S_N2 reaction	RSM 2.60
	Zn*	Reagent/catalyst/solvent/time	Reaction conditions	
1	✓	LiCl, CuCN, IC≡CTMS THF, 24 h	X	Degradation
2	✓	$Pd_2(dba)_3$, Sphos, DMF IC≡CTMS, rt, 18 h	X	81%
3	X	$Bu_3SnC{\equiv}CH$, $Pd_2(dba)_3$, *o*-tolylphosphine, DME, rt, 24 h	X	38%
4	X	$Bu_3SnC{\equiv}CH$, $Pd_2(dba)_3$, *o*-tolylphosphine, MeCN, 80 ºC, 24 h	X	69%
5	X	X	NaC≡CH, HMPA, THF, -78 ºC-rt 24 h	Only SM[a]
6	X	X	LiC≡CTMS, CuI, THF, -30 ºC-rt o/n	30%
7	X	X	BrMgC≡CH, CuI, -30 ºC, THF, 24 h	Only SM[a]

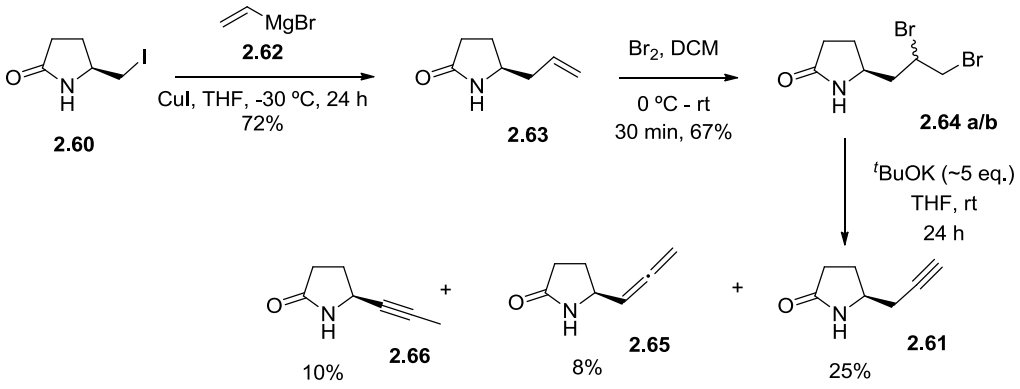
Table VI – Attempts to convert iodide 2.60 into alkyne 2.61. [a] Analysis of the crude reaction mixture by NMR.

In view of the results described in the previous section, it was decided to do a more detailed study on the insertion of the alkyne motif. The reaction substrate was obtained from alcohol **2.52** which was converted into iodide **2.60** *via* a

Finkelstein reaction,[103] followed by investigation of different reagents to transform iodide **2.60** into the desired alkyne **2.61** (Scheme 50, Table VI).

The first reaction attempted with iodide **2.60** was the use of zinc insertion followed by acethynylation, mediated by the use of stoichiometric LiCl and CuCN (transmetallation of organozinc to organocuprate *in situ*) (entry 1).[106] In contrast to what was observed with the 6-membered ring system (Scheme 41), the reaction degraded. Negishi[107] and Stille[114] cross couplings gave no reaction (entries 2-4), in contrast to the Negishi cross coupling on the 6-membered ring **2.1** (section 2.1.1.3) which led to decomposition of the reaction mixture. As the cross coupling reactions did not work, nucleophilic substitution reactions using NaC≡CH (entry 5), LiC≡CTMS or BrMgC≡CH mediated by CuI (entry 6 and 7) were attempted, unfortunately also without success.

2.1.2.3 Alkyne formation from the corresponding alkene



Scheme 51

Conversion of iodide **2.60** into the desired alkyne could considerably be achieved by conversion into an alkene, followed by consecutive halogenation/dehalogenation to afford the desired alkyne (Scheme 51).

Treatment of iodide **2.60** with vinyl cuprate, generated *in situ* from vinylmagnesium bromide **2.62** and copper(I) iodide, afforded alkene **2.63** in 72%,[115] which was then brominated with Br_2 affording a mixture of dibromoalkanes **2.64a/b** which could be separated by column chromatography (**2.64a** less polar isomer; **2.64b** more polar isomer).[116]

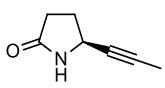
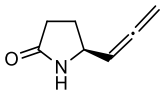
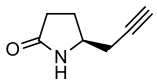
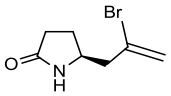
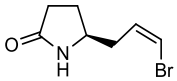
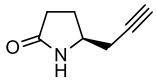
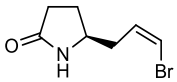
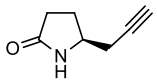
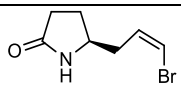
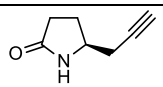
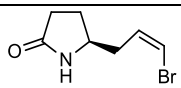
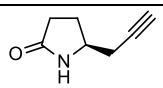
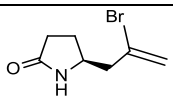
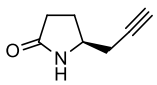
Entry	Base (eq.)	Time (h)	Temp. (ºC)	Ratio of products		
1	^{t}BuOK (4.2)	24	rt	 **2.66**	 **2.65**	 **2.61**
				0.4[a]	0.32[a]	1[a]
2	^{t}BuOK (2.5)	2.5	rt	 **2.67**	 **2.68**	 **2.61** 40%
				0.55[a]	0.35[a]	1[a]
3	^{t}BuOK (6.0)	0.5	-78	---	 **2.68**	 **2.61**
				---	1[a]	1[a]
4	^{t}BuOK (6.0)	0.8	-78	---	 **2.68**	 **2.61**
				---	1[b]	2[b]
5	^{t}BuOK (6.0)	2.75	-78	---	 **2.68**	 **2.61**
				---	1[b]	2[b]
6	LDA (6.0)	6.5	-78	 **2.67**	SM **2.64a/b**	 **2.61**
				1.4[a]	0.86[a]	1[a]

Table VII – Optimization of the dehydrobromination to obtain alkyne 2.61. [a] ratio of isolated products, [b] ratio estimated based on crude NMR

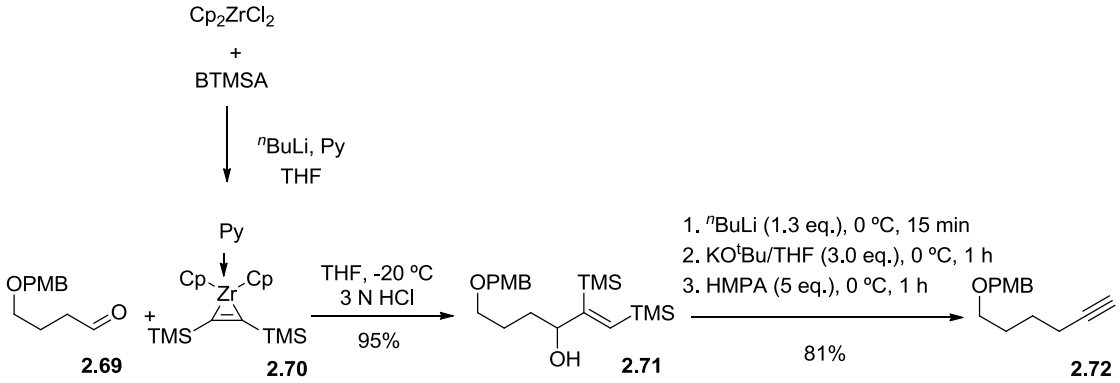
In the last step dibromalkanes **2.64 a/b** were treated with a base and what was expected to be a simple reaction was revealed to be quite complex.

Initially the less polar dibromoalkane isomer **2.64a** was reacted with ^{t}BuOK (4.2 eq.) in THF at rt (Table VII, entry 1). The reaction was monitored by TLC and after 30 min the appearance of two new compounds more polar than the starting material was observed. As the reaction was not finished, it was left to react overnight to ensure consumption of the starting material. After purification by column chromatography three compounds were isolated (Table VII entry 1).

The desired alkyne **2.61** was obtained along with two byproducts, allene **2.65** and alkyne **2.66** in the ratio of 1:0.32:0.40, respectively. These two latter products **2.65** and **2.66** are believed to be derived from isomerisation of alkyne **2.61**. With the desired compound in hand, attempts to optimise the reaction were carried out by investigating the role of base and reaction time (Table VII). Subsequent reactions (entries 2-6) were performed with a mixture of both dibromoalkenes **2.64a/b**. Decreasing both the amount of base used and the reaction time (TLC showed complete consumption of starting material after 2.5 h) resulted in three products (entry 2), which were identified as bromoalkenes **2.67** and **2.68** and the desired alkyne **2.61** in a ratio of 0.55:0.35:1, respectively. Based on literature precedent,[117] it was then decided to decrease the temperature of the reaction and increase the amount of base. Use of 6 eq. of ^{t}BuOK (entries 3-5) afforded a mixture of bromoalkene **2.68** and alkyne **2.61** that could not be separated by column chromatography. The ratio of products was 1:1 after 30 minutes and 1:2 after 50 minutes, with no further change being observed at longer reaction times. Use of LDA (entry 6) as a base also gave a mixture of products (starting material **2.64a/b**, bromoalkene **2.67** and alkyne **2.61** in 0.86:1.4:1 ratio).

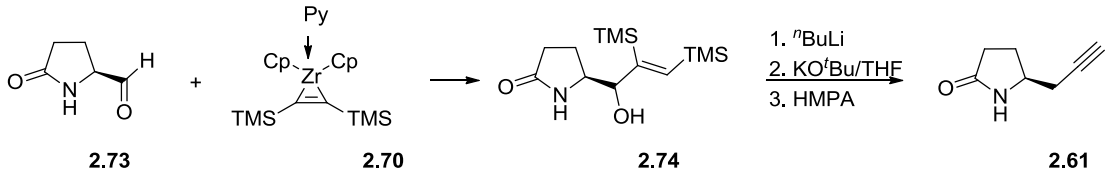
Although the desired alkyne **2.61** had been successfully obtained in moderate yield, the difficulty of separating it from side products **2.67** and **2.68** prompted investigation into alternative synthetic routes.

2.1.2.4 Towards synthesis of alkyne 2.61 by reductive ethynylation



Scheme 52

Contemporaneous to this work, a method that converted an aldehyde to an alkyne by a two carbon homologation was published by Danishefsky and co-workers.[118] A reductive ethynylation of aldehyde **2.69** was achieved by addition of the zirconia nucleophile **2.70**, obtained by hydrozirconation of BTMSA. Treatment of the resultant bistrimethylsilyl alkene intermediate **2.71** with a mixture of bases afforded selectively the desired alkyne **2.72**, via a Brook/Peterson transformation (Scheme 52).



Scheme 53

Following this approach, it was decided to apply their strategy to the synthesis of alkyne **2.61**. (Scheme 53).

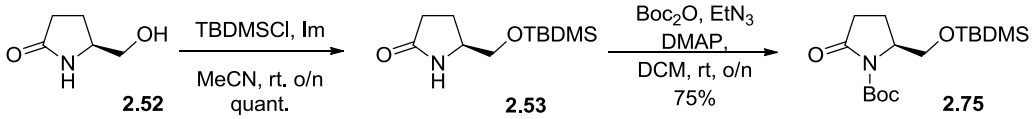
Scheme 54

Entry	Reaction conditions	Observations
1	DMP, wet DCM, rt, o/n	Degradation
2	PCC, $MgSO_4$, DCM, 2.5 h	Degradation
3	DMSO, $(COCl)_2$, DIPEA, DCM, o/n	Degradation
4	DMSO, $(COCl)_2$, DIPEA, THF, o/n	No reaction
5	IBX, DMSO, rt, 22 h	Degradation
6	IBX, DMSO, rt, 2 h	Degradation
7	IBX, MeCN, 80 ºC, 1 h	Mixture of products
8	IBX, AcOEt, 80 ºC, 3.5 h	Mixture of products
9	Tempo-Baib, MeCN, rt, 3 h	Mixture of products

Table VIII – Different reaction conditions for the oxidation of alcohol 2.52 to aldehyde 2.73.

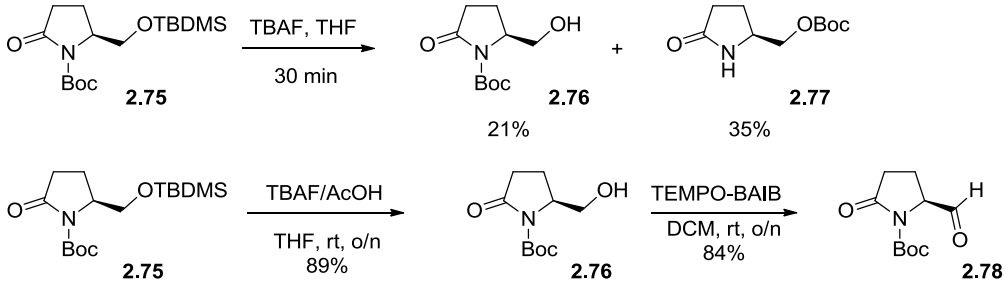
However, prior to initiation of this elegant strategy, it was necessary to oxidise the previously obtained alcohol **2.52** to the corresponding aldehyde **2.73** (Scheme 54). A range of oxidising reagents (DMP, PCC, Swern oxidation, IBX,

TEMPO-BAIB) were used, however, in all cases the reaction mixture decomposed (Table VIII). Therefore, it was decided to protect the amide nitrogen before proceeding further.



Scheme 55

To ensure chemoselectivity, the alcohol group needed to be protected first (Scheme 55). Consequently, alcohol **2.52** was protected with TBDMSCl, followed by reaction with Boc_2O and NEt_3 in the presence of DMAP, yielding the di-protected compound **2.75** in 75% yield.[119]



Scheme 56

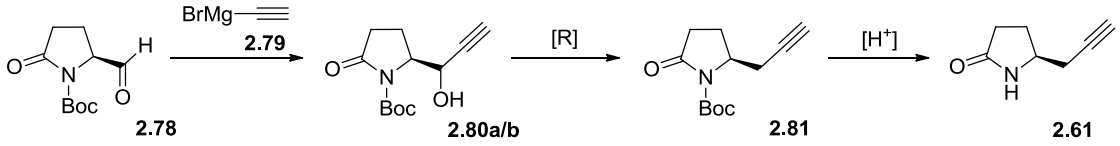
When TBAF in THF was used to deprotect the TBDMS group, the free alcohol **2.76** was only obtained in 21% yield, along with by-product **2.77** (35%) (Scheme 56), which is likely to arise from the migration of the Boc group after the cleavage of the silyl group.[120] To overcome this problem, the reaction was carried out in the presence of a small amount of acetic acid (Scheme 56) to protonate the alkoxide resulting from silyl deprotection preventing the migration of the Boc group.[120] Alcohol **2.76** was then easily oxidised to the corresponding aldehyde **2.78** (84% yield) with TEMPO-BAIB (Scheme 56),[121] confirming that the problem in the previous oxidation was the presence of the free lactam.

Finally, with aldehyde **2.78** in hand, it was possible to try the reductive ethynylation described above (Scheme 53). The zirconate intermediate **2.70** was generated *in situ* from reaction of Cp_2ZrCl_2 with BTMSA in the presence of ^{n}BuLi and pyridine. Formation of the intermediate was confirmed by observation of its characteristic deep red colour in solution. Unfortunately, when the

zirconate **2.70** was slowly added to the freshly made aldehyde **2.78**, after 30 min the molecule was completely destroyed.

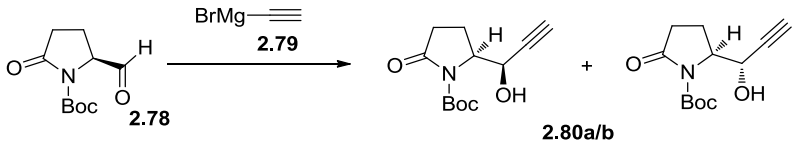
The compounds studied by Danishefsky and co-workers are in general alkyl substituted allylic alcohols (which are protected with a *p*-methoxybenzyl (PMB) group), a conjugated enal and an aromatic aldehyde. In all cases the bistrimethylsilyl alkene intermediate is formed in good yield, however there are no amides present in any of the compounds reported. In this case the bistrimethylsilyl alkene intermediate is not formed. A possible source of functional group incompatibility is the excess of the ^{n}BuLi used in the formation of the zirconate **2.70** which is likely to react with aldehyde **2.78** by addition to the aldehyde carbonyl. Less likely but possible, side reactions are addition to the amide or the Boc groups, or removal of the acidic protons at H4

2.1.2.5 Alkyne formation via Grignard addition to the aldehyde



Scheme 57

Alkyne **2.61** could also be obtained from aldehyde **2.78** via a Grignard addition of ethynylmagnesium bromide **2.79** followed by reductive removal of the alcohol **2.80a/b** (Scheme 57).



Scheme 58

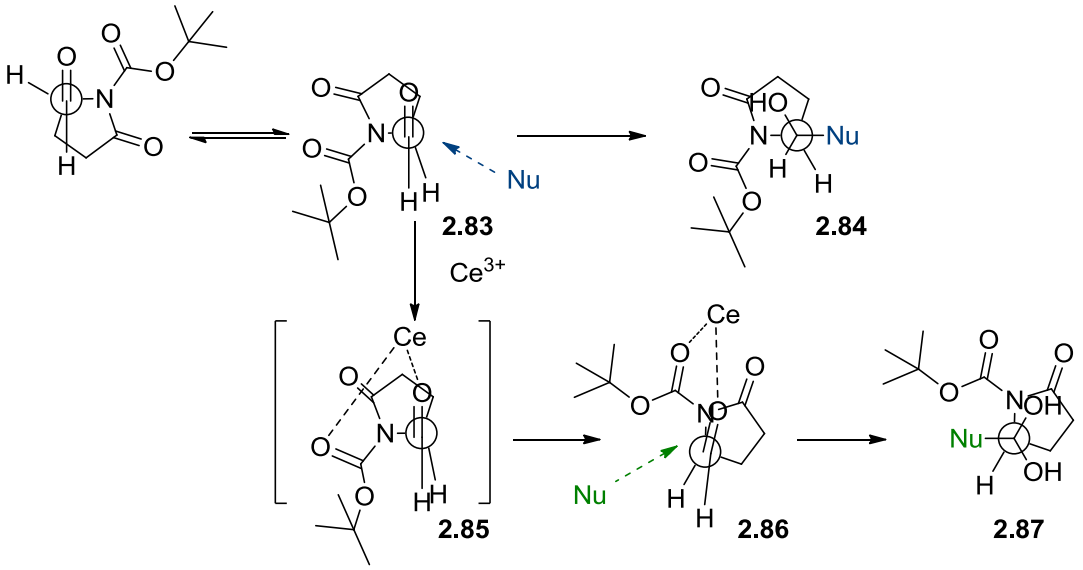
Entry	Alylating agent (eq.)	Additive (eq.)	Solvent	Temp. (ºC)	Time (h)	Yield (%)	RSM (%)	Isomer ratio 280a/b
1	BrMg (1.5)	---	THF	0 - rt	4	19	14	1:1.3[a]
2	BrMg	---	THF	0 - rt	24	---[b]	---[b]	---[b]

	(1.5)							
3	BrMg—≡ (2)	---	THF	0	1	42	---	1:1.6 [a]
4	BrMg—≡ (3)	LiCl (3)	THF	0	1.5	40	12	1:1.4 [a]
5	BrMg—≡ (3)	$BF_3{\cdot}OEt_2$ (3)	THF	0 - rt	o/n	--- [b]	--- [b]	--- [b]
6	BrMg—≡ (3)	$CeCl_3$ (2)	THF	0 - rt	6	16	17	3:1 [a]
7	BrMg—≡ (5)	---	Et_2O, dioxane	0 - rt	o/n	--- [b]	--- [b]	--- [b]
8	BrMg—≡ (5)	---	Et_2O, dioxane	-78 - rt	16	31	13	1:1.6 [a]
9	Na—≡ (3)	---	THF	-40 - rt	1	--- [b]	--- [b]	--- [b]

Table IX – Attempted optimisation of the Grignard addition to the aldehyde 2.78. [a] Isomers ratio **280a**: less polar fraction, **280b** more polar fraction, [b] degraded.

Aldehyde **2.78** was reacted with ethynylmagnesium bromide **2.79** in THF affording alcohols **280a/b** in 19% yield (as a 1:1.3 ratio of isomers, **280a** less polar isomer and **280b** more polar isomer; the stereochemistry of the diastereoisomers was not assigned) along with 14% of RSM **2.78** (Scheme 58).[122] It is well known that Grignard reactions are often accompanied by side reactions such as enolizations, reductions, condensations and conjugate additions resulting in lower yields of the desired products.[123] Accordingly, in order to optimise the reaction, the effect of solvent, temperature and additives was investigated (Table IX). Since the starting material was not all consumed in 4 h (entry 1), the reaction time was increased to 24 h (entry 2), however this led to decomposition of the reaction mixture. Use of 2 eq. of the Grignard reagent at 0 ºC gave complete reaction after 1 h and the products were obtained in 42% yield (entry 3). Addition of LiCl to the Grignard reaction had no effect (entry 4). LiCl and $BF_3{\cdot}OEt_2$ are Lewis acids known to coordinate with carbonyl groups to make them more electrophilic for Grignard additions, but in this case they did not help to improve the product yield.

$CeCl_3$ is also a known additive for these type of reactions by forming an organocerium complex that is generally less basic than the parent Grignard and is a stronger nucleophile.[123,124]

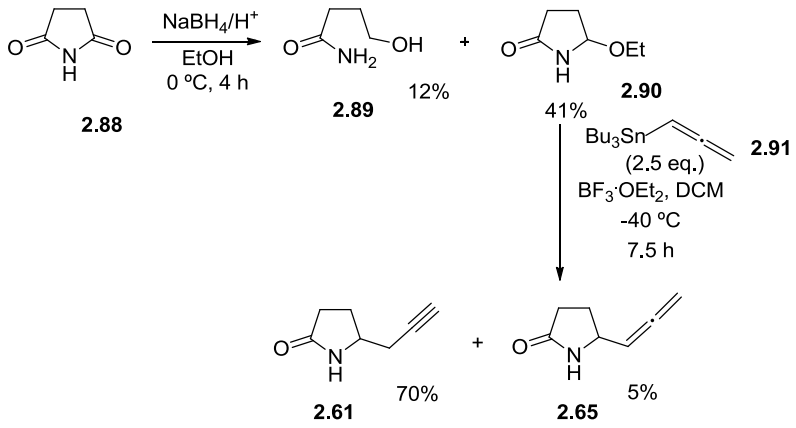


Scheme 59

It is noteworthy that although the addition of $CeCl_3$ does not increase the yield of the products, the ratio in which the products were obtained changed from ~1:1.5 to 3:1 (see Table IX). This can be explained based on the chelation transition state that can form by the lone pairs of the nitrogen and the carbonyl co-ordinating the cerium ion when $CeCl_3$ is used (Scheme 59).[123] Usually, when there are no atoms that can coordinate, the nucleophile will attack the less hindered face in the transition state (blue arrow in Scheme 59). On the other hand, in the presence of a metal that is able to chelate, in order for the coordination to occur, the molecule has to rotate affording a different conformation in the transition state. Addition of the nucleophile at the less hindered face of the new transition state (green arrow in Scheme 59), would afford a different isomer.

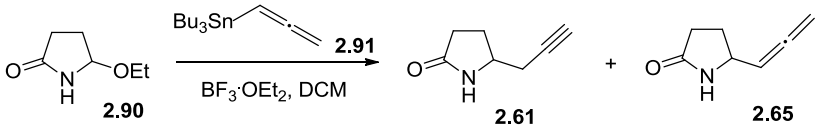
The Grignard reaction did not afford the expected results. As a consequence it can be concluded that the addition of additives does not increase the reaction yield. As low yields were obtained and the products were difficult to isolate from the reaction mixture, no further work was carried out in respect to this approach.

2.1.2.6 Synthesis of racemic alkyne from succinimide



Scheme 60

There is precedent for racemic alkyne **2.61** being obtained from the reaction of allenylstannanes with ethoxylactams derived from succinimide.[125] Partial reduction of succinimide **2.88** with sodium borohydride in ethanol, followed by ethanolysis at pH ~3-4 of the intermediate *N,O*-hemiacetal afforded ethoxylactam **2.90** in 41% yield (Scheme 60). In the original report[126] the yield for ethoxylactam **2.90** was 88%, however in this work after many attempts the product was never obtained in such a good yield. The same problem was also reported by Sy and co-workers.[127] Furthermore, it was observed that compound **2.89** was obtained as a side product, resulting from over-reduction of the intermediate.

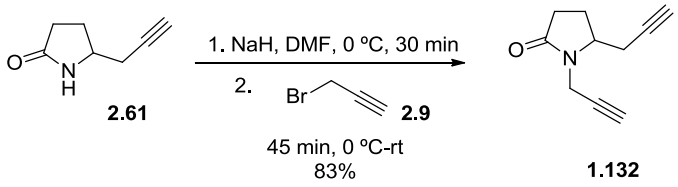


Scheme 61

Entry	scale (mg)	2.91 (eq.)	Time (h)	Temp. ºC	Yield (%)		
					2.90	2.61	2.65
1	100	1.2	2	0-rt	trace	38[a]	trace
2	100	1.5	2	-40	✓[b]	✓[b]	trace
3	50	2.5	7	-40	---	70[c] (32)[a]	5
4	200	2.5	7.5	-40	---	60[c] (47)[a]	5

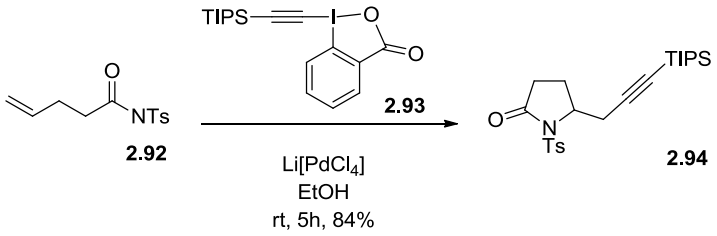
Table X – Formation of racemic alkyne 2.61 with allenyltin 2.91 in DCM with 2 eq. of $BF_3{\cdot}OEt_2$. [c] isolated yield, [b] 1:1 ratio **2.61**/**2.65** analysis of crude NMR, [c] estimated yield by NMR.

The next step was formation of racemic alkyne **2.61** (Scheme 61). This reaction has been reported as producing an excellent yield (94%) for a six-membered ethoxylactam.[125] In this system, ethoxylactam **2.90** was reacted with tributylallenylstannane **2.91** (1.2 eq.) (Table X, entry 1), and the target racemic alkyne **2.61** was obtained in 38% yield. Recovered SM and the corresponding allene **2.65** were also observed in trace quantities. Due to the low yield obtained, it was decided to subject the ethoxylactam **2.90** to other reaction conditions. The reaction was slower when it was performed at -40 ºC even with a slight increase in the amount of the allenyltin **2.91** (entry 2). When stopped after 2 h, the ratio between SM **2.90** and alkyne **2.61** was 1:1. This reaction proved to be difficult to purify as both the SM **2.90** and product **2.61** had the same R_f, meaning that the reaction had to be forced to completion to facilitate isolation of the product. Accordingly, 2.5 eq. of allenyltin **2.91** was used and the reaction time extended. ^{1}H NMR spectroscopy of the crude product revealed that all the SM **2.90** had reacted. Purification of the reaction mixture proved to be difficult, due to the polarity of racemic alkyne **2.61** and the corresponding allene **2.65** once again being very similar.



Scheme 62

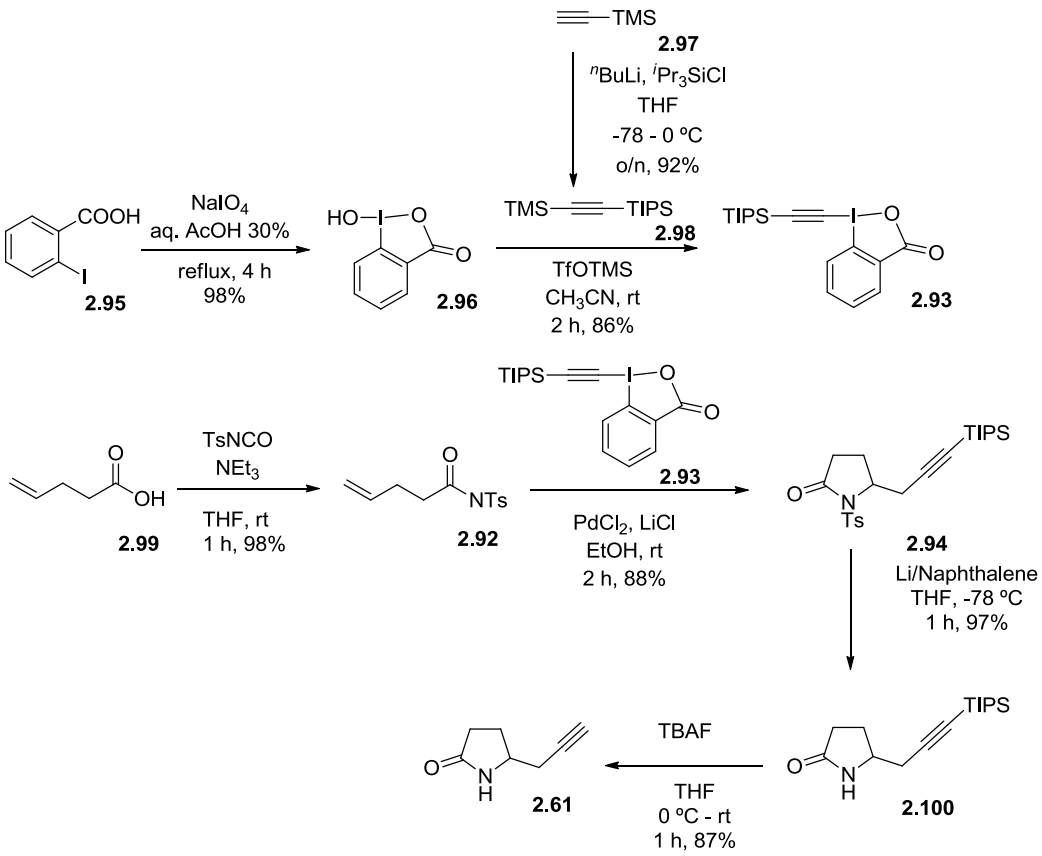
With alkyne **2.61** in hand, dialkyne **1.132** was easily prepared (83% yield) with NaH and propargyl bromide in DMF (Scheme 62).



Scheme 63

During the course of the work on the transition-metal catalysed [2+2+2] cyclotrimerisation studies, an alternative route to the synthesis of the racemic

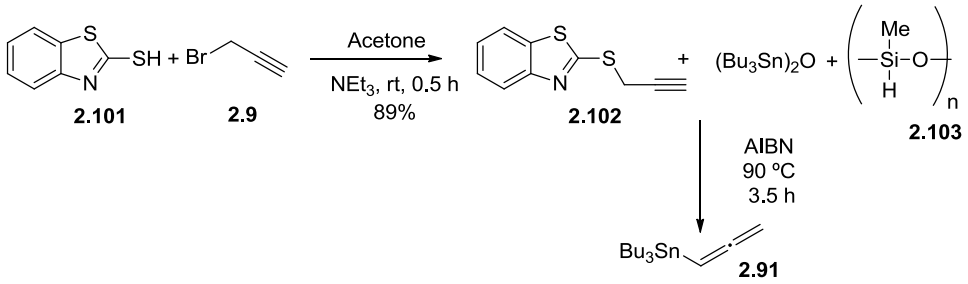
alkyne **2.61** was published. Nicolai and co-workers reported an intramolecular aminoalkynylation of olefins with a hypervalent iodine reagent catalysed by a lithium palladate catalyst (generated *in situ*) (Scheme 63).[128] This is an interesting alternative to the previous synthesis mainly because it would avoid the use of tin, which is very toxic and carcinogenic. Nicolai and co-workers mention that there are several factors that make this method widely applicable including the use of inexpensive LiCl, $PdCl_2$ (the most common palladium catalyst) and triisopropylsilylethynyl-1,2-beziodoxol-3(1H)-one (TIPS-EBX), which is commercially available. However, the drawback is that this commercially available hypervalent iodine is expensive (£134/g), although it can be synthesised in a good yield over three steps.



Scheme 64

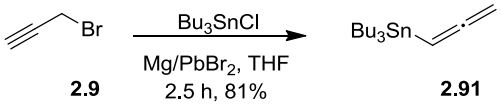
Comparing this method to the one presented in Scheme 60, it involves more steps for the synthesis of lactam **2.61** (Scheme 64), making this route less viable (7 steps compared with 4).

2.1.2.6.1 Synthesis of tributylallenyltin



Scheme 65

Allenyl tin **2.91** can be synthesised from 2-mercaptobenzothiazole **2.101** (Scheme 65).[129] As such, 2-mercaptobenzothiazole was reacted with propargyl bromide to afford alkylated compound **2.102** in 89% yield after recrystallisation. However, the reaction of alkyne **2.102** with tributyl tin oxide and polysiloxane in the presence of azobisisobutyronitrile (AIBN) was prone to polymerisation during the reaction itself or on purification of the product.

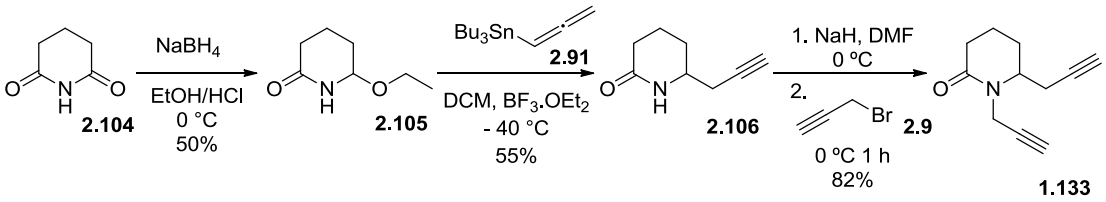


Scheme 66

Therefore, allenyl tin **2.91** was prepared via a Grignard reaction, Scheme 66. Propargyl bromide **2.9** was added to a solution of tributyl tin chloride, magnesium and a substoichiometric amount of lead bromide in THF, yielding the desired compound **2.91** in 81% yield after purification by column chromatography on alumina.[130]

Obtaining tributylallenyl tin **2.91** in high yield allowed the scale-up of the synthesis of **1.132** and therefore start the [2+2+2] cyclotrimerisations of the key alkyne intermediates (section 2.2). However, before discussing these investigations, the synthesis of two more compounds as substrates for the cyclotrimerisations is reported.

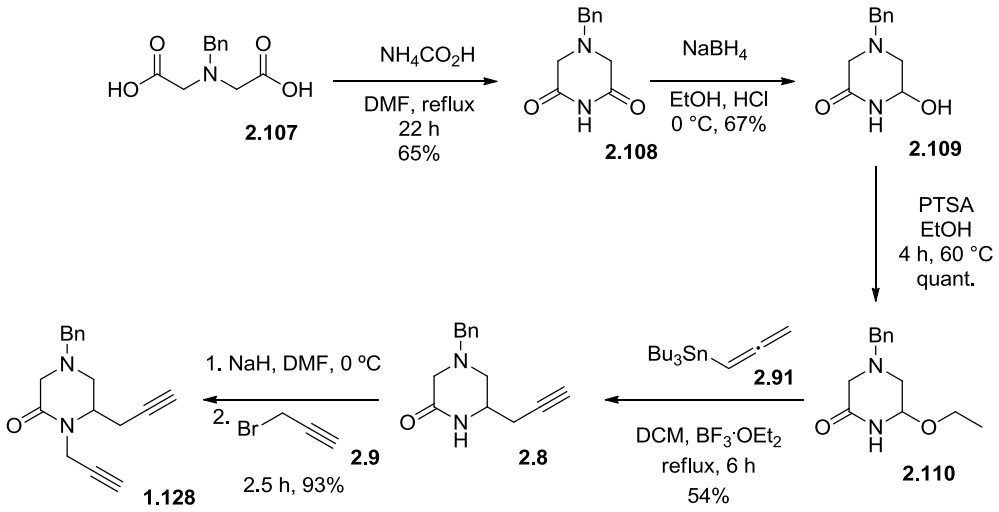
2.1.3 Synthesis of racemic 1,6-di(prop-2-yn-1-yl)piperidin-2-one



Scheme 67

Following the synthesis used for dialkyne **1.132**, glutarimide **2.104** was partially reduced with sodium borohydride in HCl/EtOH to give the corresponding ethoxy lactam **2.105**.[125] Reaction with allenyl tin **2.91** afforded monoalkyne **2.106** in 55% yield. Treatment of monoalkyne **2.106** with sodium hydride and propargyl bromide **2.9** afforded the desired 6-membered ring dialkyne **1.133** in 82% yield (Scheme 67).

2.1.4 Synthesis of racemic 4-benzyl-1,6-di(prop-2-yn-1-yl)piperazin-2-one



Scheme 68

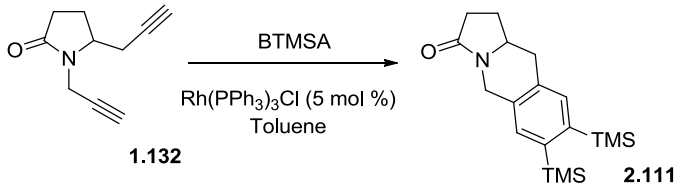
Unsuccessful approaches towards the synthesis of (*S*)-4-benzyl-1,6-di(prop-2-yn-1-yl)piperazin-2-one **1.128** have already been outlined (section 2.1.1). Since it was very important to obtain this dialkyne to produce model THIQ tricyclic

adducts by [2+2+2] cyclotrimerisation, it was decided to apply the synthetic route of dialkyne **1.132** towards molecule **1.128** (Scheme 68).

Imide **2.108** was synthesised from *N*-benzyliminodiacetic acid **2.107**, which underwent ring closure with ammonium formate in refluxing DMF yielding the corresponding imide **2.108** in 65% yield.[131] Partial reduction of lactam **2.108**, applying the same conditions used for lactam **2.88** (Scheme 60), afforded alcohol **2.109** (67% yield) instead of ethoxylactam **2.110**. Alcohol **2.109** was converted to the desired ethoxy lactam **2.110** in quantitative yield by heating in ethanol with substoichiometric *p*-toluenesulphonic acid (PTSA). Reaction of ethoxylactam **2.110** with allenyltin **2.91** did not go to completion at temperatures between -40 ºC and rt. When the reaction was performed at reflux in DCM product **2.8** was obtained in 54% yield. Alkylation of alkyne **2.8**, was done easily with NaH and propargyl bromide, affording dialkyne **1.128** in 93% yield.

2.2 Transition-metal catalysed [2+2+2] cyclotrimerisation of alkynes

2.2.1 Studies on the [2+2+2] cyclotrimerisation of 1,5-di(prop-2-yn-1-yl)pyrrolidin-2-one 1.132

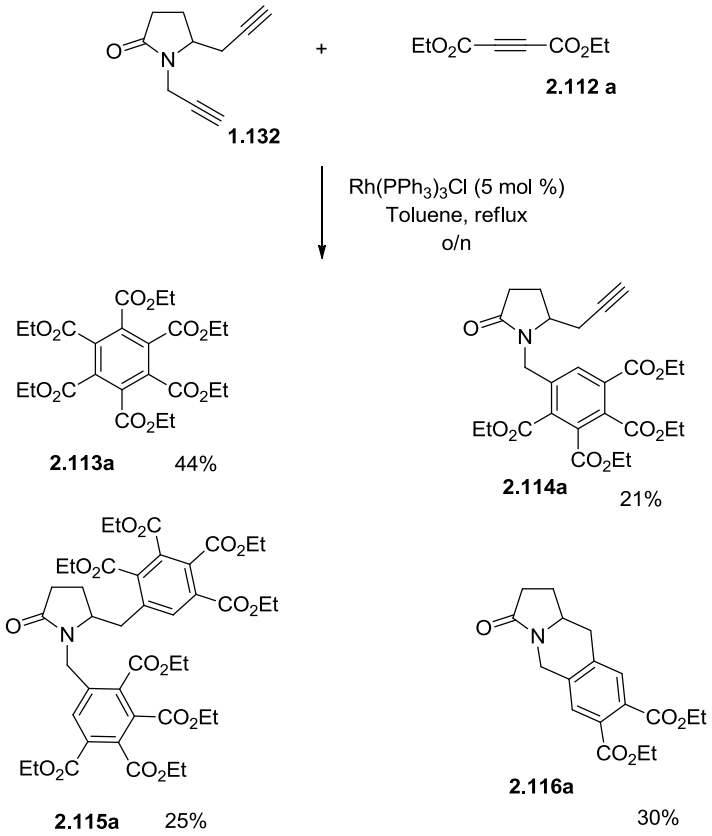


Scheme 69

Entry	Temp. (ºC)	Time (h)	Yield 2.111
1	reflux	o/n	0 [a]
2	rt	24	0 [b]
3	50	14	0 [b]
	reflux	o/n	0 [a]

Table XI – Attempted reactions for the cyclotrimerisation of dialkyne 1.132 and BTMSA. [a] Unidentified mixture of products, [b] Did not react.

Investigation of the transition-metal catalysed [2+2+2] cyclotrimerisation of alkynes started with investigation of the reaction of dialkyne **1.132** and BTMSA (an alkyne commonly used in this type of cyclisation) catalysed by Wilkinson's catalyst (Scheme 69, Table XI).[132] However, the expected cyclisation did not take place as dialkyne **1.132** did not react at either rt or 50 ºC. Indeed, it only seemed to react at reflux in toluene where it afforded a mixture of unidentified products.



Scheme 70

Entry	Catalyst (mol %)	Temp (ºC)	Solvent	Time (h)	yield (%)			
					2.113[a]	**2.114**	**2.115**	**2.116**
1	A 5	reflux	Toluene	18	44	21	25	30
2	A 5	reflux	Toluene[b]	7	---[c]	---[c]	---[c]	---[c]
3	A 5	reflux	Toluene[d]	5.5	7	[e]	[e]	17
4	A 10	reflux	Toluene	2.5	---[c]	---[c]	---[c]	---[c]

5	B 10	reflux	Toluene	4	11	4	8	42
6	B 10	rt	DCE	24	---[f]	---[f]	---[f]	---[f]
7[g]	B 10	reflux	Toluene	4	11	3	7	44
8[g]	B 5	reflux	Toluene	8.5	14	2	8	15
9[g]	B 10	50	Toluene	Incomplete after 3 days				
10[g]	B 10	100	Toluene	24	10	1	7	15
11[g]	B 10	reflux	Dioxane	8.5	7	6	5	29
12[g]	B 10	reflux	Benzene	9	8	3	4	2
13[g]	B 10	reflux	THF	24	10	2	4	14
14[g,h]	B 10	reflux	Toluene	24	8	trace	3	27
15[g,i]	B 10	reflux	Toluene	19	2	---	---	45
16	C[j] 10	reflux	Toluene	6.5	32	18	7	18
17	D 10	reflux	Toluene	2.5	24	trace	16	70

Table XII – Optimisation of tricyclic adduct 2.116 synthesis. Reactions performed with 0.310 mmol of dialkyne **1.132**, 5 eq. of diethyl acetylenedicarboxylate **2.112a** in 2 mL of solvent. Catalyst: A - $RhCl(PPh_3)_3$, B – $CpCo(CO)_2$, C - $[Ir(cod)Cl]_2$, D – Cp*Ru(cod)Cl. [a] yield based on the amount of diethyl acetylenedicarboxylate **2.112a** used, [b] Pre-mixing of $RhCl(PPh_3)_3$ with dialkyne **1.132** followed by syringe addition of diethyl acetylenedicarboxylate **2.112a**, [c] degradation, [d] syringe addition of diethyl acetylenedicarboxylate **2.112a**, [e] mixture **2.114**:**2.115** 1:15, [f] did not react, [g] stock solution of catalyst (0.23 M), [h] 2.5 eq. diethyl acetylenedicarboxylate **2.112a**, [i] 1 eq. of diethyl acetylenedicarboxylate **2.112a** and 2 eq. of dialkyne **1.132**.[j] DIPHOS 10 mol%.

Next, the reaction of diethyl acetylenedicarboxylate **2.112a** with **1.132** was investigated under the same reaction conditions. The desired tricyclic product **2.116a** was obtained in 30% yield along with the hexasubstituted benzene **2.113a** resulting from trimerisation of monoalkyne **2.112a** (44%) and two other products, compound **2.114a** (21%) and compound **2.115a** (25%) which resulted

from the reaction of two molecules of monoalkyne **2.112a** and the individual alkyne branches on dialkyne **1.132** (Scheme 70). NMR spectroscopy revealed that, for compound **2.115a**, the cyclotrimerisation happened on the alkyne branch attached to the nitrogen. In this structure the NC*H*H' and NCH*H*' are more deshielded (4.17 and 5.10 ppm) than in the starting material (3.67 and 4.55 ppm). The ^{13}C NMR spectrum of products **2.114a** and **2.115a** and their corresponding derivatives often show superimposition of the CH_3 and OCH_2 carbons, nevertheless it can be confidently stated that it is the right compound; all other characterisation matches the desired structure.

As shown in Table XII, it can be seen that the chemoselectivity of Wilkinson's catalyst for dialkyne **1.132** is quite low, i.e., the ability for the catalyst to coordinate preferencially with dialkyne **1.132** is very low, which explains all the by-products formed. Table XII summarises attempts to optimise the reaction of dialkyne **1.132** with diethyl acetylenedicarboxylate **2.112a** in order to increase chemoselectivity. The formation of **2.113a** could have arisen from the addition of diethyl acetylenedicarboxylate **2.112a** into the reaction vessel as a bolus, providing a high localised concentration to co-ordinate with the catalyst and trimerise. However, pre-mixing of Wilkinson's catalyst with dialkyne **1.132**, followed by syringe addition of monoalkyne **2.112a** over 7 h, led to decomposition of the reaction mixture (entry 2) and addition of diethyl acetylenedicarboxylate **2.112a** over a period of 5.5 h did not increase the amount of product **2.116a** (entry 3).[44] When Vollhardt's catalyst (10 mol %) was used the desired tricyclic adduct **2.116a** was obtained in 42% yield (entry 5) with a corresponding decrease in the amount of by-products formed. A stock solution of catalyst was used during this study to minimise catalyst exposure to air and allow accurate dispensing of small quantities. It was confirmed that the use of a stock solution did not affect the yield of the reaction (entry 7). The literature reports high yields from similar reactions using DCE as a solvent at rt.[43] However, dialkyne **1.132** did not react under these conditions (entry 6). Decreasing either the catalyst loading (entry 8) or reaction temperature (entries 9 and 10) decreased the reaction rate and overall yield of product **2.116a**. To investigate the stability of dialkyne **1.132** during the course of the reaction, a reaction was carried out using an excess of dialkyne **1.132** (ratio dialkyne/monoalkyne 2:1) (entry 15). Compound **2.116a** was obtained with the same yield as before (45% yield) and 53% of the starting monoalkyne **2.112a**

was recovered. However, because twice the amount of dialkyne **1.132** was used it means that 75% of the compound **1.132** had decomposed.

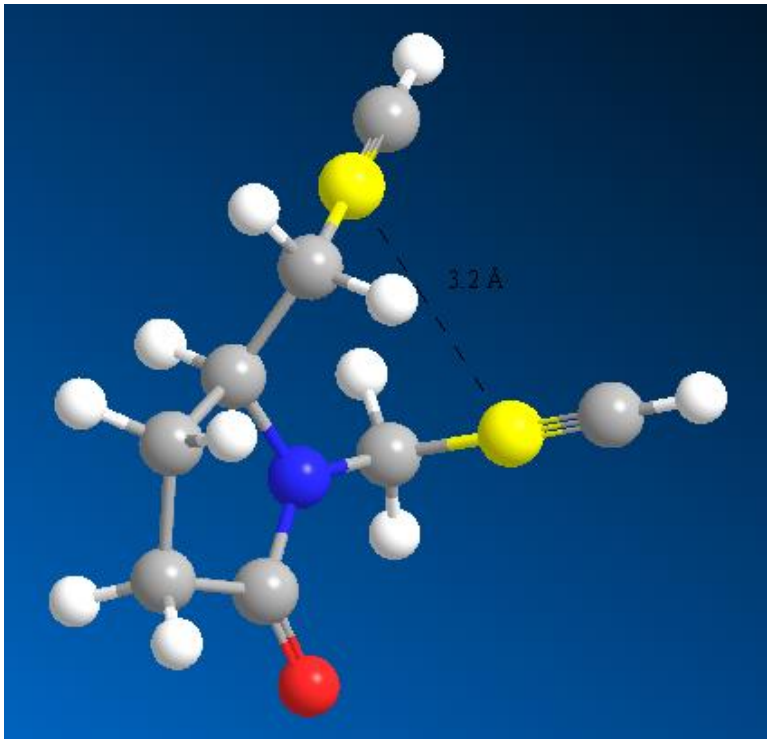


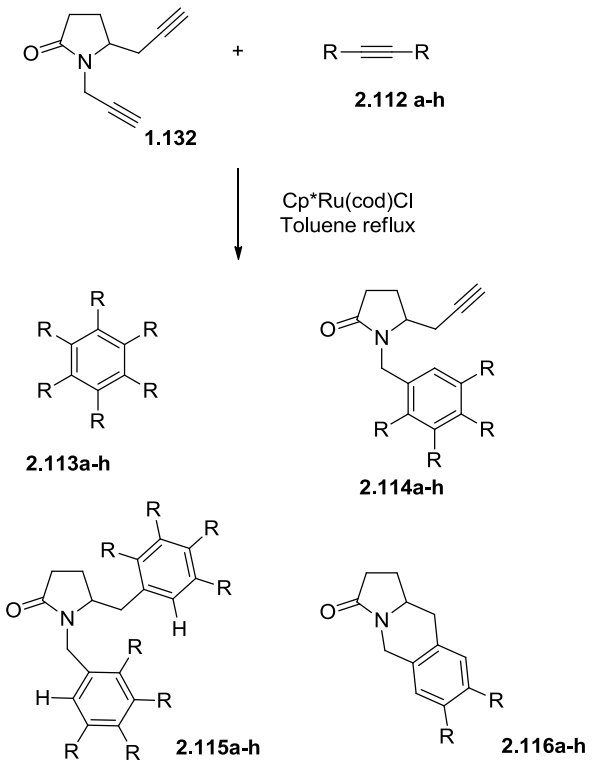
Figure 17 – Minimised energy conformation in vacuum for dialkyne 1.132. * Structures modeled using *ChemBio3D* and minimised to give the lower energy state.

Examining the minimum energy conformation of dialkyne **1.132** can suggest why there is the need for higher temperatures. In the lowest energy conformation (Figure 17) the two alkynes are not in close proximity (3.2 Å distance between the reactive carbons atoms) when compared with the average C-C bond distance (1.5 Å). Therefore, it is likely that the reaction will not occur unless more energy is put into the reaction system to allow it to access higher energy conformations where the two alkyne branches are close enough in order to coordinate efficiently to the catalyst.

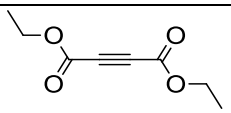
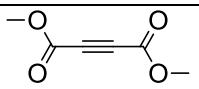
In summary, for this reaction system Vollhardt's catalyst is more chemoselective than Wilkinson's catalyst for the formation of tricyclic adduct **2.116a**. It has also been shown that the yield of product **2.116a** decreases with reduction of the catalyst loading, the temperature of reaction and the amount of monoalkyne **2.112a** used. The best solvent is toluene at refluxing temperature.

The attempts to optimise the reaction of dialkyne **1.132** with diethylacetylene **2.112a** in the presence of Vollhardt's catalyst were not successful, therefore in

an attempt to increase product formation, two more catalysts ($[Ir(cod)Cl]_2$ and Cp*Ru(cod)Cl) were used with the same monoalkyne system (entries 16 and 17). $[Ir(cod)Cl]_2$ is widely used in [2+2+2] cyclotrimerisation reactions[41], and here it was used in the presence of DIPHOS affording the product **2.116a** in 18% yield. Although, it did not increase the product formation, it notably altered the ratio of byproducts obtained, affording byproduct **2.114a** in higher yield compared with byproduct **2.115a**, which did not occur before. It is possible that the presence of a bulky ligand that coordinates with the metal limited the second addition to the alkyne branch of compound **2.114a**. When Cp*Ru(cod)Cl was used as the catalyst under refluxing toluene it afforded the desired product **2.116a** in very good yield, making this catalyst the most chemoselective of the four catalysts used.



Scheme 71

Entry	Monoalkyne 2.112a-h	Time (h)	Yield (%)			
			2.113[a]	2.114	2.115	2.116
1	**a** 	2.5	24	trace	16	70
2	**b** 	1	22	---	17	34

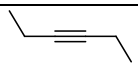
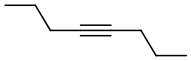
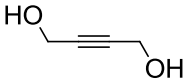
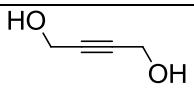
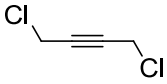
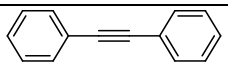
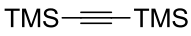
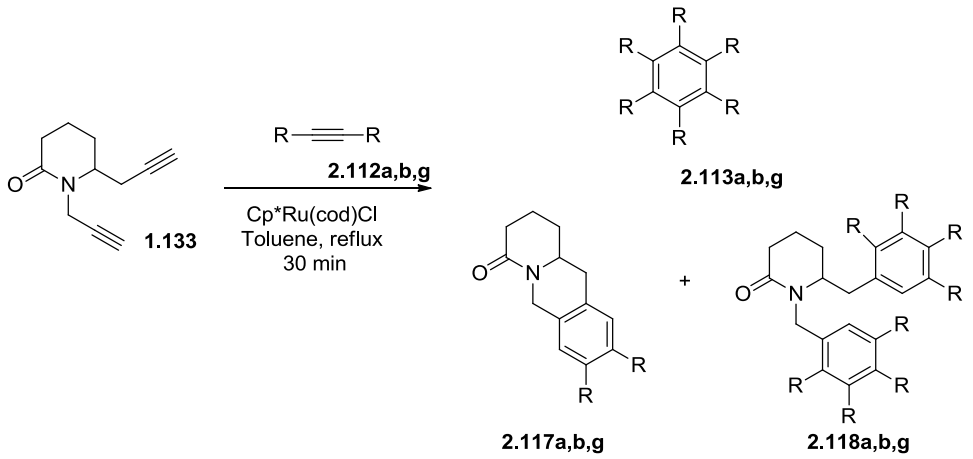
3	**c** 	20	Degradation			
4	**d** 	20	Degradation			
5	**e** 	4 days	Did not react			
6	**e** 	3 days[b]	Did not react			
7	**f** 	24	Degradation			
8	**g** 	24	32	---	---	trace
9	**h** 	24	Degradation			

Table XIII – Monoalkyne screening. Reactions performed with 0.310 mmol of dialkyne **1.132**, 5 eq. of monoalkyne in 2 mL of toluene under reflux with 10 mol % of Cp*Ru(cod)Cl. [a] yield based on the amount of monoalkyne used, [b] reaction carried out in DMF at 110 ºC.

Having identified an effective catalyst for the [2+2+2] cyclotrimerisation, the next step was to investigate the reactivity of dialkyne **1.132** with monoalkynes **2.112a-h** (Scheme 71, Table XIII), in order to explore the steric and electronic effects of the substituents.

The monoalkyne screening showed that electron withdrawing monoalkynes are more reactive towards [2+2+2] cyclotrimerisation (entries 1, 2 and 8, Table XIV) whereas the electron donating monoalkynes (entries 3-6 and 9) led to decomposition of the reaction mixture. Alkyne **2.112e** did not seem to be soluble in toluene and the reaction formed two phases even after four days under reflux conditions; dialkyne **1.132** did not react or decompose (entry 5). Subsequently, the reaction was repeated in DMF at 110 ºC (entry 6). Although the problem of solubility was overcome, the problem of reactivity remained, even after 3 days there was no product formed. BTMSA **2.112h** did not react with dialkyne **1.132** in the presence of Cp*Ru(cod)Cl or as previously shown with Wilkinson´s catalyst; this was quite disappointing because BTMSA is widely used in [2+2+2] cyclotrimerisations of alkynes due to the absence of competition for the homotrimerised product.[56]

2.2.2 [2+2+2] Cyclotrimerisation of 1,6-di(prop-2-yn-1-yl)piperidin-2-one 1.124



Scheme 72

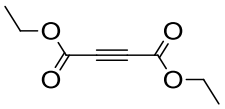
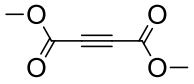
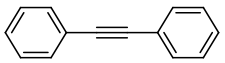
Entry	Monoalkyne 2.112	Time (h)	Yield (%)		
			2.113	2.117	2.118
1	a 	0.5	19	46	8
2	b 	1	26	28	8
3	g 	24	31	5	--

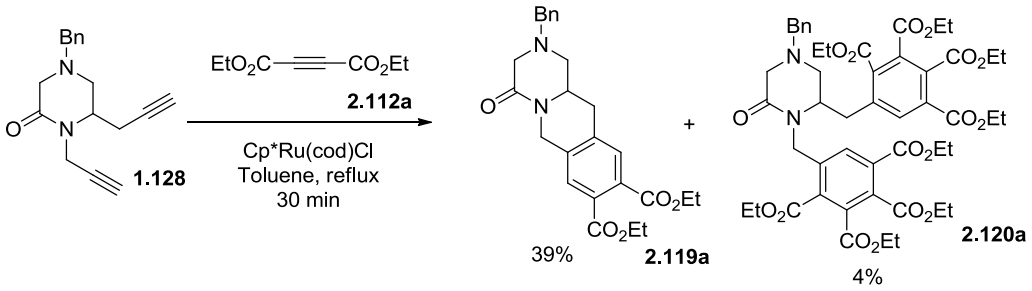
Table XIV - **Monoalkyne screening.** Reactions were performed with 0.310 mmol of dialkyne **1.133**, 5 eq. of monoalkyne in 2 mL of toluene under reflux with 10 mol % of Cp*Ru(cod)Cl. [a] yield based on the amount of monoalkyne used.

Monoalkynes **2.112a**, **b** and **g** were most reactive with dialkyne **1.132**, therefore they were used in subsequent reactions with the 6-membered ring dialkyne **1.133** under the previously optimised reaction conditions using Cp*Ru(cod)Cl as the catalyst in refluxing toluene.

The 6-membered ring scaffold dialkyne **1.133** gave a similar pattern of results compared to the 5-membered ring **1.132** (Scheme 72 and Table XIV). Better yields were obtained with the diethyl ester than the corresponding methyl ester.

Diphenylacetylene was much lower yielding; although it is an electron withdrawing alkyne, there might be a steric clash associated with the insertion of this alkyne to the metallacycle adduct during the catalytic cycle (see Scheme 3 in section 1.4.1.1).

2.1.3 [2+2+2] Cyclotrimerisation of 4-benzyl-1,6-di(prop-2-yn-1-yl)piperazin-2-one 1.119



Scheme 73

Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	NMR % yield	
					2.119a	1.128
1	Cp*Ru(cod)Cl	Toluene	reflux	0.5	39[a]	**--**
2	Cp*Ru(cod)Cl	Toluene	reflux	0.5	32	--
3	Cp*Ru(cod)Cl	DCE	rt	24	10	75
4	Cp*Ru(cod)Cl	DCE	reflux	24	12	59
5	Cp*Ru(cod)Cl	Toluene	rt	24	25	60
6	Cp*Ru(cod)Cl	Toluene	40	72	26	40
7	Cp*Ru(cod)Cl	Toluene	60	5	37	--
8	Cp*Ru(cod)Cl	Toluene	100	5	38	--
9	Cp*Ru(cod)Cl	DCE/Toluene 1:1	85	24	28	10
10	Cp*Ru(cod)Cl	DMF	85	24	7.3	--[b]
11	$Pd(PPh_3)_4$	Toluene	reflux	2.5	--[b]	--[b]

Table XV – Optimisation of the [2+2+2] reaction conditions for dialkyne 1.128. Reactions performed with 0.310 mmol of dialkyne **1.128**, 5 eq. of monoalkyne **2.112a**, 40 mol % of 1,3,5-trimethoxybenzene in 2 mL of toluene under reflux with 10 mol % of Cp*Ru(cod)Cl. [a] isolated yield; [b] degraded.

The last dialkyne substrate to be studied in the [2+2+2] cyclotrimerisation reactions of alkynes was 4-benzyl-1,6-di(prop-2-yn-1-yl)piperazin-2-one **1.128**. Dialkyne **1.128** was reacted with diethyl acetylenedicarboxylate **2.112a** (5 eq.) and Cp*Ru(cod)Cl (10 mol %) in refluxing toluene, affording 39% yield of the desired cycloadduct **2.119a** along with 4% of by-product **2.120a** (Scheme 73, Table XV, entry 1). Quantitative NMR spectroscopy was used to estimate the yield of the products during optimisation of the reaction of dialkyne **1.128**. 1,3,5-trimethoxybenzene was selected as the internal standard, because this compound generates two singlets in the ^{1}H NMR spectrum: one at 6.02 ppm which corresponds to the three aromatic hydrogens and another at 3.75 ppm which corresponds to the three methoxy groups, both of which do not overlap with the peaks of product **2.119a**. Additionally, 1,3,5-trimethoxybenzene is non-volatile, so can be included in reactions under reflux, and samples can be concentrated without risk of losing the internal standard. To prove that the transition-metal catalysed cyclotrimerisation reaction was not affected by the addition of the internal standard, dialkyne **1.128** was reacted with diethyl acetylenedicarboxylate **2.112a** (5 eq.) and Cp*Ru(cod)Cl (10 mol %) in refluxing toluene, affording 39% yield of the desired cycloadduct **2.119a** along with 4% of by-product **2.120a** (Scheme 73, Table XV, entry 1). Next, dialkyne **1.128** was reacted with diethyl acetylenedicarboxylate **2.112a** under the same conditions with the addition of 40 mol % of 1,3,5-trimethoxybenzene (entry 2). On completion of the reaction, the toluene was removed under vacuum and a ^{1}H NMR spectrum of the crude reaction mixture was recorded, which was analysed to give an estimated yield of 32% of product **2.119a**. It can be stated that the yield estimated by NMR spectroscopy is an acceptable approximation of the isolated yield (isolated yield of 38% vs NMR yield of 32%), which indicates that the internal standard does not affect the course of the reaction. Next, attempts to optimise this reaction were performed and the results are shown in Table XV. The best solvent for this reaction was found to be toluene at reflux (entry 1). The use of lower temperatures resulted in decreased yields and extended reaction times (entries 5-8). Use of DCE instead of toluene gave even lower yields than reactions in toluene at the same temperatures (entries 3 and 4), and the use of DMF caused substantial decomposition (entry 10). It is noticeable that a maximum yield seems to be reached for a particular set of reaction conditions, i.e. ~10% for reactions in DCE, 25% for those in toluene below 60

°C and 38% for those in toluene above 60 °C. Increasing the reaction time or temperature within these conditions only decreased the amount of SM recovered rather than increasing the yield. This suggests that the product may be decomposing as the reaction progresses.

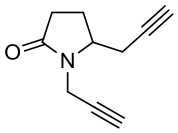
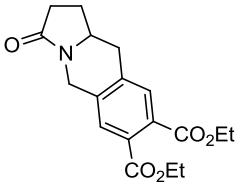
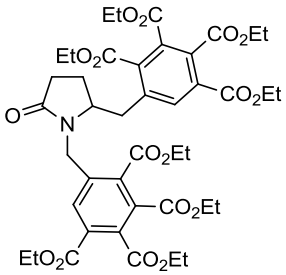
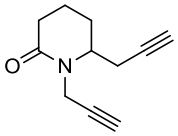
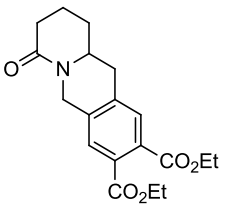
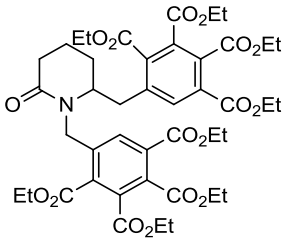
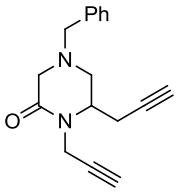
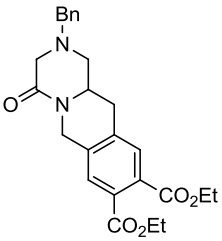
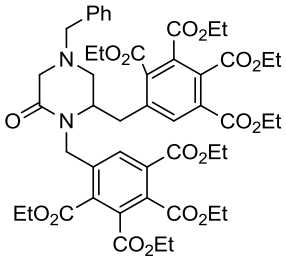
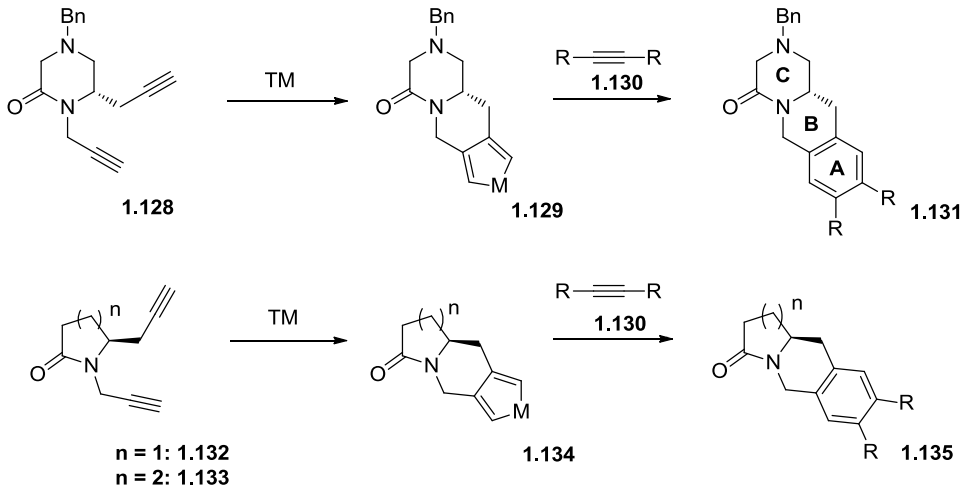
Entry	Dialkyne	Product (% yield)	By-product (% yield)
1	 **1.132**	 **2.116a** 70%	 **2.115a** 16%
2	 **1.133**	 **2.117a** 46%	 **2.118a** 8%
3	 **1.128**	 **2.119a** 38%	 **2.120a** 4%

Table XVI – Products and by-products obtained from the reaction of dialkynes 1.132, 1.133 and 1.128 with diethylacetylene dicarboxylate 2.112a (5 eq.) catalysed by Cp*Ru(cod)Cl (10 mol %) under reflux toluene.

Comparing the [2+2+2] cyclotrimerisations of the three substrates (1,5-di(prop-2-yn-1-yl)pyrrolidin-2-one **1.132**, 1,6-di(prop-2-yn-1-yl)piperidin-2-one **1.133** and 4-benzyl-1,6-di(prop-2-yn-1-yl)piperazin-2-one **1.128**) when reacting with diethylacetylene dicarboxylate **2.112a** and Cp*Ru(cod)Cl in refluxing toluene, reaction of **1.132** is higher yielding than reaction of either of the 6-membered ring dialkynes, and **1.132** also produced more of the byproduct resulting from intermolecular cyclotrimerisation of each alkyne sidechain. This suggests the

configuration most frequently adopted by dialkyne **1.132** holds the two alkyne branches closer, allowing it to react faster and affording a better yield of **2.116a**. There was no significant difference in reactivity between the piperidinone and piperazinone skeletons.

2.3 Conclusions



Scheme 22

Three dialkynes, **1.132**, **1.133** and **1.128** have been prepared using amide reduction and aminal substitution to introduce one propargyl sidechain, followed by amide N-alkylation with propargyl bromide to introduce the second.

The study of the transition-metal catalysed [2+2+2] cyclotrimerisation of alkynes started with dialkyne **1.132**. Several reaction conditions were screened and the best conditions found was using diethylacetylene dicarboxylate **2.112a** as the monoalkyne, Cp*Ru(cod)Cl as the catalyst and toluene as the solvent under refluxing conditions to afford tricyclic compound **2.116a** in 70% yield. With this optimised reaction condition, other monoalkynes were reacted with dialkyne **1.132**. It was concluded that electron withdrawing alkynes react efficiently with dialkyne **1.132**, since the reaction mixture decomposed when electron donating monoalkynes were employed. Dialkynes **1.133** and **1.128** afforded the expected tricyclic adducts **2.117a** and **2.119a** when reacted with diethylacetylene dicarboxylate **2.112a,** albeit in lower yield.

Chapter 3 Diversity-oriented small library synthesis *via* transition-metal catalysed [2+2+2] cyclotrimerisations under microwave irradiation

3.1 Microwave Assisted Organic Synthesis

Radiation	Quantum Energy (eV)	Bond type	Bond Energy (eV)
γ-Rays	1.24×10^{6}	C-C	3.61
X-Rays	1.24×10^{5}	C=C	6.35
UV	4.1	C-O	3.74
Visible	2.5	C=O	7.71
IR	0.012	C-H	4.28
Microwave	0.00126	O-H	4.80
Radio waves	4.0×10^{-9}	Hydrogen Bond	0.04-0.44

Table XVII – Radiation energies compared to bond energies.[133]

Microwave radiation is an electromagnetic radiation located between the infrared and radio frequency waves, with a wavelength of between 1 cm and 1 m (0.3 GHz to 300 GHz). Domestic and industrial microwave ovens operate at 2.45 GHz which corresponds to 0.00126 eV of energy. Such a low energy is unable to cleave C-C bonds (3.61 eV) or hydrogen bonds (0.04-0.44 eV) (Table XVII), therefore microwave radiation itself is not capable of initiating chemical reactions.[134,135,136]

First reported by Gedye in 1986[137] and later by Giguere and Majetich,[138] microwave assisted organic synthesis (MAOS) uses microwave radiation to dramatically accelerate the rate of the reactions, reducing the reaction times from days to hours to seconds, enhancing the yields and improving reproducibility. It is a powerful tool in organic synthesis, as it accelerates the rate of the reaction; high temperatures are reached in a few seconds, therefore reactions are shorter and cleaner, with less side products. The reaction is not controlled or limited by the boiling point of the solvent, since superheating

conditions can be achieved within closed vessels, for example methanol can be heated to temperatures above 100 ºC.

MAOS is an established method used in many labs in academia and industries and it appears as an alternative to the use of isomantles, oil baths and hot plates and other energy sources (ultrasonic, high pressure and plasma) and it has often been used in different areas of chemistry not only in organic but also in medicinal and combinatorial chemistry and also in biochemistry[139,140] In the early days of the application of microwaves in organic synthesis, domestic microwave ovens or cavities designed for analytical science were used, however, problems associated with the use of flammable solvents, safer containers and reproducibility of results (accurate power and temperature measurements) led to equipment improvements. Nowadays microwave reactors are equipped with built-in magnetic stirring, temperature, power and pressure controls as well as cooling options (CO_2 or N_2 streams), and automation. The cooling option is very important since it allows that the bulk heating generated inside the reaction mixture is minimized by the use of simultaneous cooling in order to avoid thermal degradation of certain substrates.

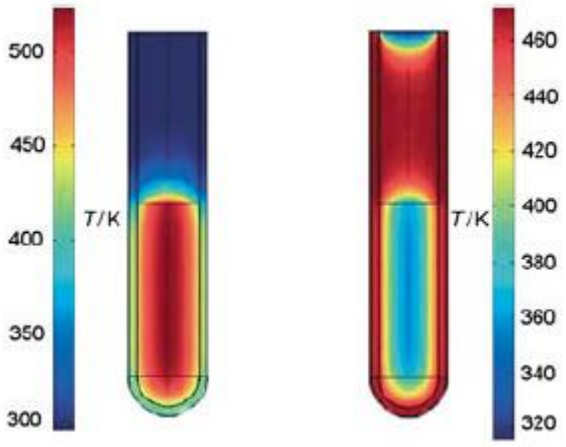


Figure 18 – Inverted temperature gradients in microwave heating (left) versus conventional heating (right). Temperature profiles (finite element modeling) after 1 min are shown for both heating methods. In microwave the temperature of the whole volume is raised simultaneously (bulk heating, left), whereas in a conventional heating tube the reaction mixture in contact with the vessel wall is heated first (right).[134]

Conventional thermal heating is usually slow and is associated with inefficient energy transfer, being dependent on the conductivity of the reaction vessel and on convection currents of the solvents resulting in a heterogeneous distribution of heating in the reaction mixture (Figure 18 right). Usually the temperature of the oil bath is 20-50 ºC higher than the internal temperature of the reaction mixture and sometimes reagents (mainly catalysts) can decompose in contact with the vessel wall. Conventional heating is usually limited by the boiling point of the solvent, unless the reaction is done in a sealed tube, which can present the risk of explosion of vessels under pressure.[141]

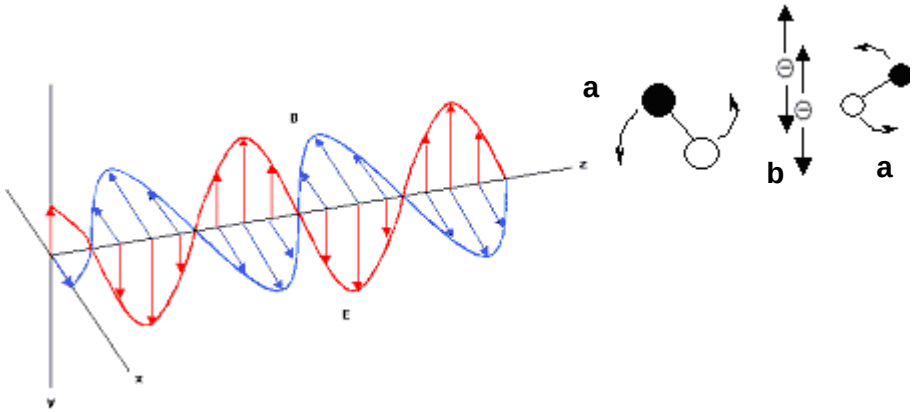


Figure 19 – Dipoles and ions trying to align with the applied electric field by rotation (a. dipoles) and by moving back and forth (b. ions).

Microwave heating (also named as microwave dielectric heating) transforms electromagnetic radiation into heat, by taking advantage of the properties of materials (liquids and solids) in absorbing microwave radiation. Like all types of radiation, microwave radiation has an electric and a magnetic component, and it is the electric component that is responsible for the heating. Microwave dielectric heating depends on two mechanisms: dipolar polarisation and ionic conduction.[142,143] In dipolar polarisation, when an electric field is applied to a system the molecules (induced or permanent dipoles) will tend to align with the field by rotation. As the electric field oscillates the molecules rotate with it (Figure 19 a), however they cannot always change orientation at a rate equal to the field's which induces friction and collisions between molecules ultimately leading to heating. In ionic conduction, microwave energy is absorbed by ions, that will also move back and forth with the electric field (Figure 19 b). The kinetic

energy will increase due to collisions between ions and other molecules and energy is released in the form of heat.

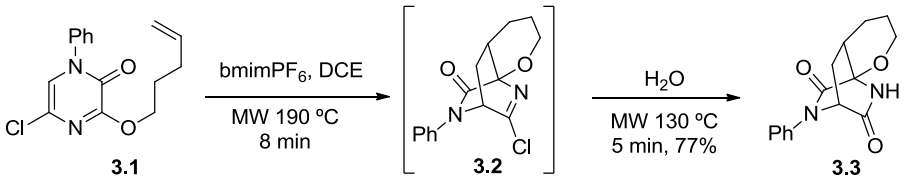
Solvent	tan δ	Solvent	tan δ
Ethylene glycol	1.350	DMF	0.161
Ethanol	0.941	1,2-dichoroethane	0.127
DMSO	0.825	Water	0.123
2-propanol	0.799	Chlorobenzene	0.101
Formic acid	0.722	Chloroform	0.091
Methanol	0.659	Acetonitrile	0.062
Nitrobenzene	0.589	Ethyl acetate	0.059
1-butanol	0.571	Acetone	0.054
2-butanol	0.447	THF	0.047
1,2-dichlorobenzene	0.280	DCM	0.041
NMP	0.275	Toluene	0.040
Acetic acid	0.174	Hexane	0.020

Table XVIII – Loss factors (tan δ) of different solvents.[136]

The ability of a material (reagent, catalyst or solvent) to convert microwave radiation into dielectric heating is determined by the loss tangent (tan δ) at a determined temperature and frequency. Solvents are considered as high absorbents when tan $\delta > 0.5$ and weak when tan $\delta < 0.1$, so the higher the tan δ is the more efficient the heating (Table XVIII), however, this does not mean that weak absorbent solvents cannot be used in MAOS. For weak absorbing solvents, polar additives such as ionic liquids, or passive heating elements can be added.[144] Dielectric heating does not depend on the conductivity of the reaction vessel (usually made of a material transparent to microwave radiation such as quartz, borosilicate glass or Teflon (where tan $\delta < 0.01$) but on radiation interacting directly with the reaction mixture, therefore affording a higher degree of temperature homogeneity (bulk heating, Figure 18 left).

Sometimes differences are observed in reaction rate and product distribution when MAOS is compared to conventional heating. Despite all the work published using MAOS, there is still a big controversy on why and how microwave enhances chemical reactions. Initially it was thought that these differences were only due to specific or non-thermal microwave effects as a consequence of the radiation-material interaction (which would decrease the

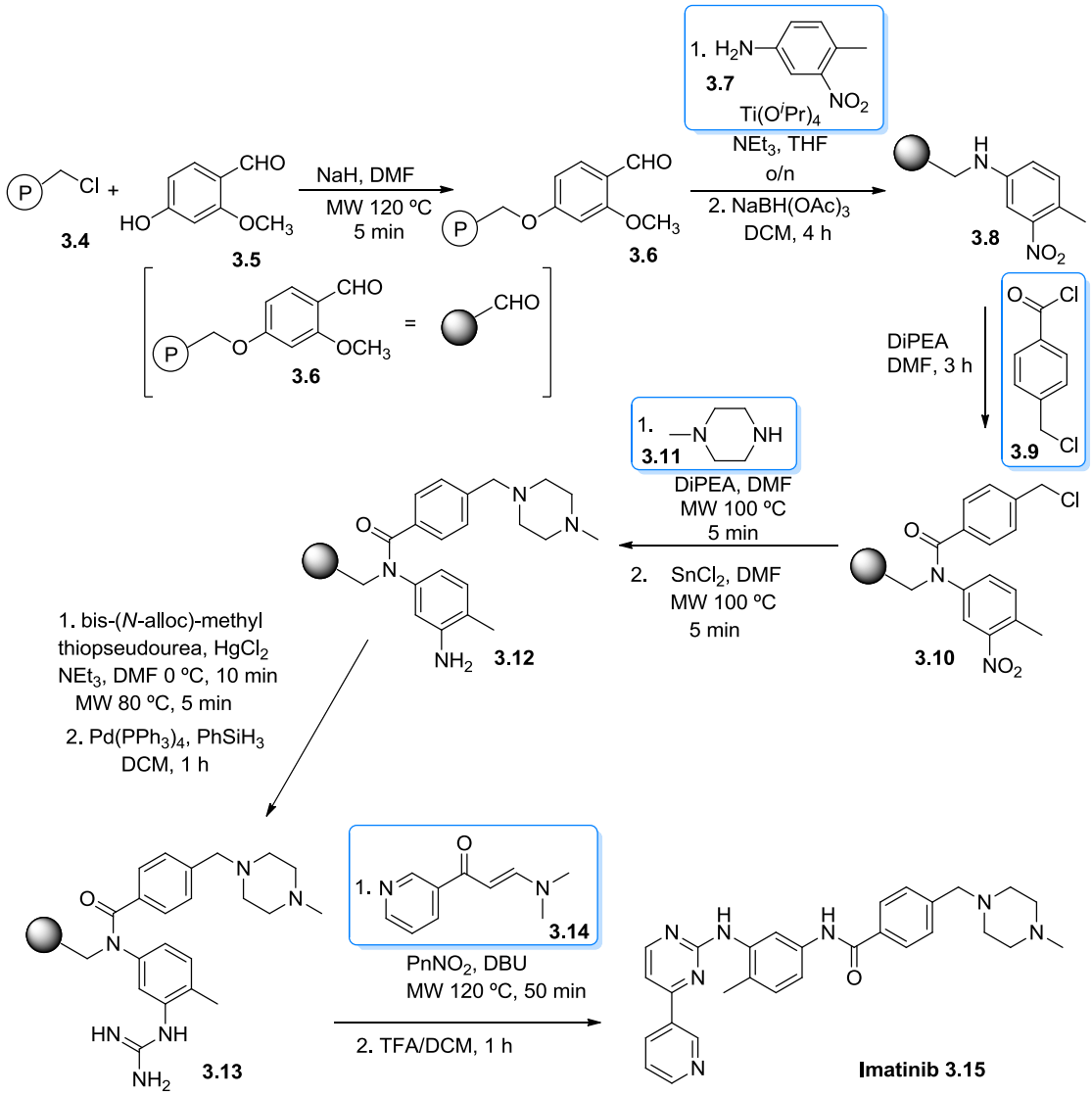
activation energy or increase the pre-exponential factor in the Arrhenius equation). Nowadays most researchers appear to agree that the main reason is just based on thermal/kinetic effects due to reaching elevated temperatures more quickly. The Arrhenius equation [$k = Aexp(-\frac{Ea}{RT})$] relates reaction rate to temperature of the system: reactions that take hours at reflux temperatures will be finished in just a few minutes in superheated solvents.



Scheme 74

MAOS has a wide application in different reactions such as organometallic (Heck, Suzuki, Stille cross coupling), cyclisations (Diels-Alder, RCM), heterocyclic (indoles, pyrroles, quinolines, quinolones, furans, lactams), oxidations, reductions, condensations, nucleophilic additions (Michael additions, Mitsunobu reactions) amongst others.[145,146] The example described in Scheme 74 illustrates the influence of the temperature and the solvent on the reaction rate of an intramolecular hetero Diels-Alder reaction.[144] Under conventional heating the reaction was done in refluxing PhCl (bp 132 ºC) over 24 h to obtain product **3.2**. Under microwave irradiation, the reaction took 1 h to completion in DCE (bp 83 ºC) (reaching a maximum temperature of 170 ºC). With addition of a small amount of an ionic liquid (bmimPF_6) to improve absorption of radiation, the reaction mixture reached 190 ºC in less than 1 minute and the reaction was finished in just 8 minutes. Microwave irradiation was also used to reduce the time for the hydrolysis step, which took place under standard conditions at rt in wet chloroform over 18 h (74%). After the first step under microwave irradiation, water was added and the reaction mixture heated for an additional 5 minutes at 130 ºC, affording compound **3.3** in 77% yield. Although both methods afford similar yields, it can be seen that using MAOS the time is reduced from 2 days to 13 minutes being a one-pot reaction in a microwave. This approach also shows how a low absorbing solvent can be combined with ionic liquids to give an enhanced reaction rate.

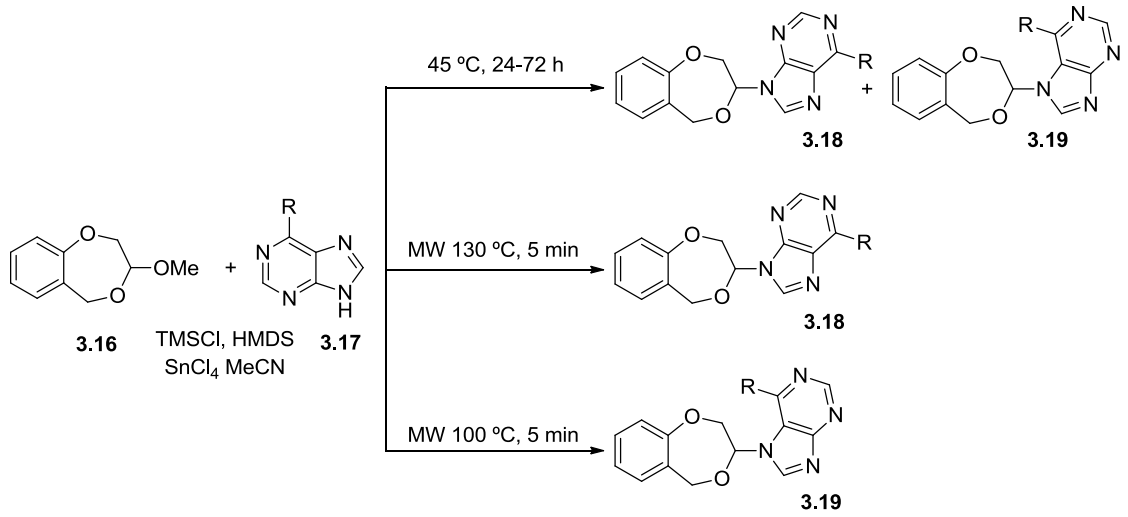
MAOS is a tool that has also been applied in drug discovery for NCEs. Some examples of its use in pharmacologically active scaffolds are shown below. (For reviews of synthesis of pharmacological scaffolds using MAOS see[147,148,149,150,151])



Scheme 75

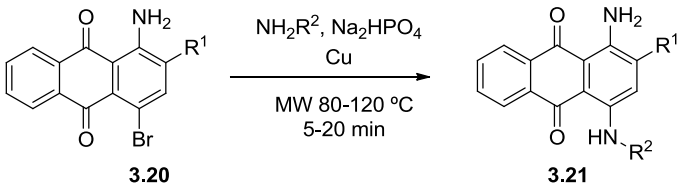
MAOS in combination with solid-phase synthesis was used for the multi-step synthesis of Imatinib **3.15** (Gleevec), an anticancer drug approved by FDA (Scheme 75).[152] Carroti and co-workers described the synthesis of Imatinib **3.15** applying microwave irradiation in 5 steps of the synthesis, which includes preparation of the linker **3.6**, nucleophilic substitution, reduction of the nitro group, formation of guanidine **3.13** and cyclisation to obtain the final product **3.15**. It is noteworthy that using MAOS, **3.13** was obtained in both higher yield

and purity and the cyclisation reaction time was reduced from 20 h to 50 minutes when compared to conventional heating. This elegant synthesis also opens the possibility for library preparation with molecular diversity as depicted in Scheme 75 in blue.



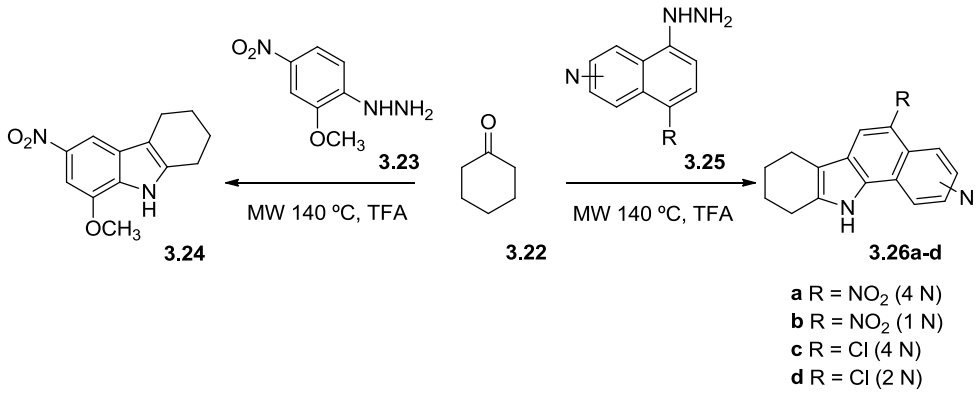
Scheme 76

Conejo-García and co-workers investigated the synthesis of purine-based compounds to be used as cyclin dependant kinase (CDK) inhibitors that are associated with cancer and degenerative diseases.[153] The authors used a one-pot Vorbrüggen condensation of cyclic acetal **3.16** and purine bases **3.17** which formed a mixture of isomers **3.18** and **3.19** using conventional heating (Scheme 76). However, when using microwave irradiation, if the temperature was controlled (100 or 130 ºC), each isomer could be selectively formed.



Scheme 77

Müller and co-workers have synthesised a small library of anthraquinone derivatives as antagonists of platelet $P2Y_{12}$ receptors.[154] As a key step, an Ullman coupling reaction of 1-amino-4-bromoanthraquinone **3.20** derivatives was employed with different anilines. The short reaction times (5-20 minutes) allowed for the synthesis of diverse derivatives in up to 90% yield.



Scheme 78

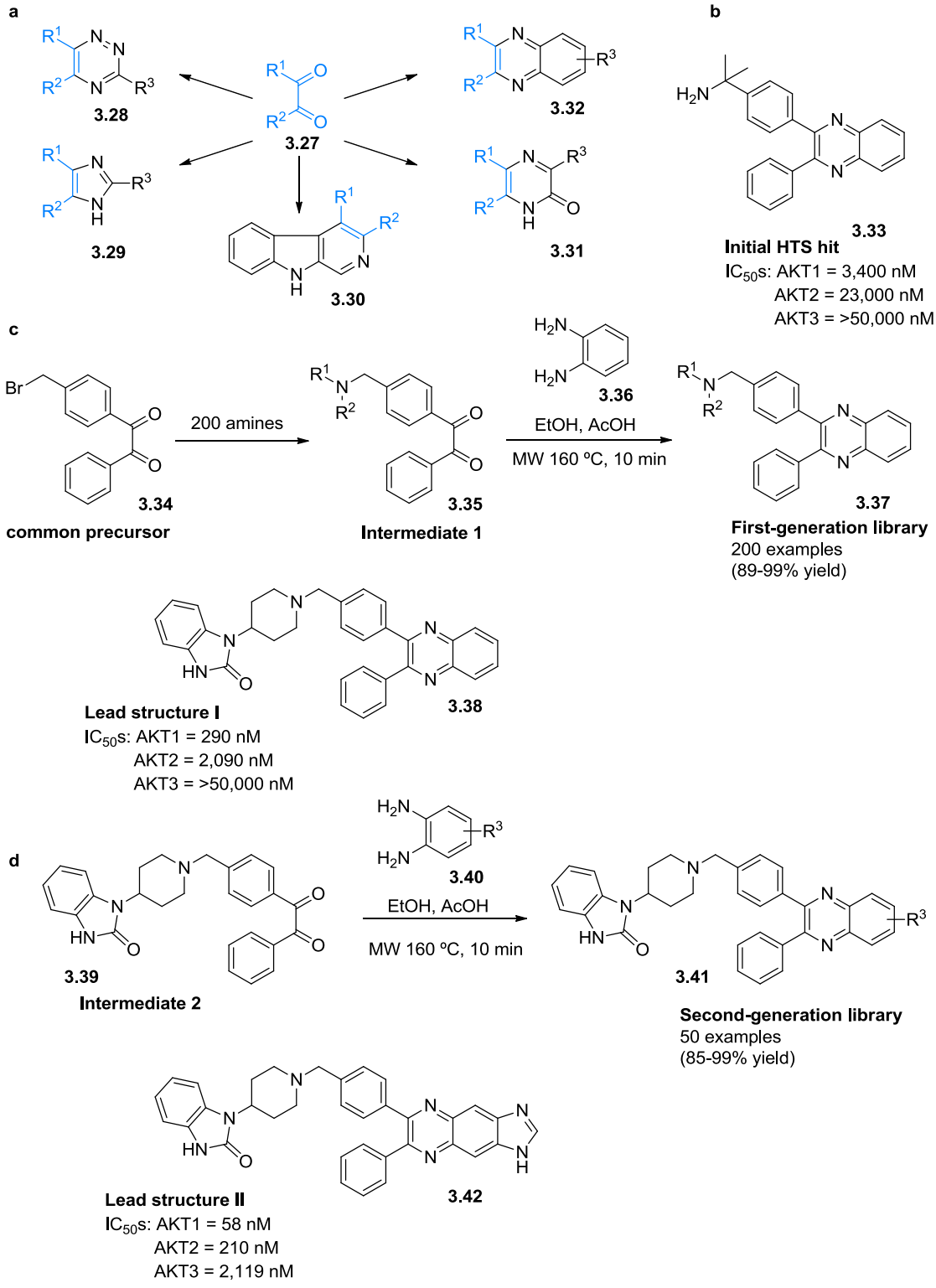
Compound	Time MW (min)	Yield MW (%)	Time conv. (h)	Yield conv. (%)
3.24	3	80	8-10	36
3.26a	3	78	4-5	53
3.26b	3	80	4-5	62
3.26c	3	95	4-5	53
3.26	3	95	4-5	48

Table XIX – Time and yield comparison between microwave (MW) and conventional heating (conv.) for indole synthesis 3.24 and 3.26a-d.

Microwave irradiation has been used to shorten the reaction times in Fischer indole synthesis, while considerably improving the yield when comparing to conventional heating (Scheme 78, Table XIX).[150] The reaction carried out by microwave is a one-pot synthesis compared with a two step conventional method.

The examples above show how microwave irradiation is helpful in the synthesis of small libraries of compounds. However, MAOS also plays an important role in big biological library synthesis when applied to high-throughput microwave synthesis: automated sequential library synthesis (integrated robotic devices with a single-mode microwave cavity) and parallel microwave library synthesis (reactions usually done in 96-well microtitre plates).[155,156]

The use of MAOS influences at least three stages of drug discovery: library generation, conversion of hits to leads and leads optimisation.[155]



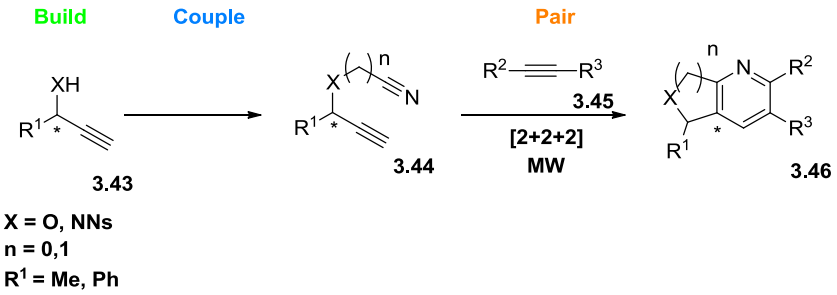
Scheme 79

Condensation of 1,2-diketones **3.27** with the appropriate partner can afford 1,2,4-triazines, imidazoles, fused pyrazines (for example, quinoxalines), pyrazin-2(1*H*)-ones and canthine derivatives in only 5-10 minutes in high yield under microwave irradiation, compared to 30-65% yield in 8-24 h with conventional heating (Scheme 79 a).[155] One of these compounds (**3.33**) was

found to be a hit against AKT (serine/threonine kinase) which regulates the apoptotic machinery of cells and plays a crucial role in cancer therapy (Scheme 79 b). To perform structure-activity relationship (SAR) studies and hit-to-lead conversion, a library of 200 compounds was quickly synthesised using MAOS; therefore bromomethyl functionalised 1,2-dicarbonyl building block **3.34** was reacted with 200 different amines followed by treatment of each intermediate **3.35** with 1,2-diaminobenzene **3.36** under microwave irradiation generating 200 different products **3.37** (Scheme 79 c). After HTS, lead I **3.38** was identified and a ten-fold increase in potency was observed in relation to the initial hit **3.33**, however due to poor solubility a second-generation library was developed with the aim of modifying the quinoxaline ring. Intermediate 2 **3.39** was treated with 50 different 1,2-diarylamines **3.40** affording 50 different products **3.41** (Scheme 79 d), which were screened against AKT to identify compound **3.42** as a lead structure II with improved potency, solubility and cell permeability.

In summary, these examples show how important the use of microwaves is in organic and medicinal chemistry/chemical biology. Its major advantages are shorter reactions times and the high temperatures that it can operate. With shorter reaction times it is possible to quickly screen different parameters in order to optimise a reaction.

3.2 Strategy design

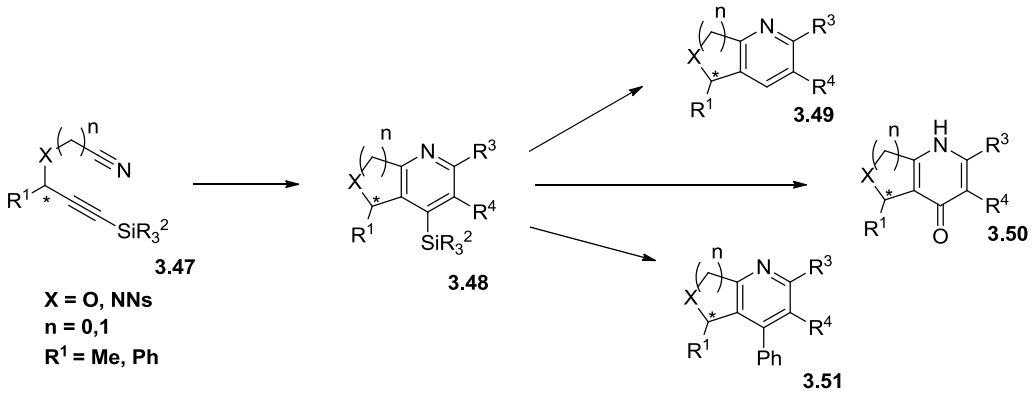


Scheme 80

Previously it was shown how DOS contributes to the development of new drugs or NCEs (section 1.2). It was also shown how applying a B/C/P strategy can lead to stereo and skeletally diverse small molecules in a quick and efficient way (up to 5 steps).

Here it was envisaged to synthesise small bicyclic systems using the B/C/P strategy described in Scheme 80. Contrary to chapter 2, retrosynthetic analysis is not needed, because there is no specific target, it is important to develop a robust method that gives as much diversity as possible.

Therefore, the building blocks in Scheme 80 were commercially available (in the case of X = O) or synthesised in one step (X = Ns), they were then coupled with an alkyne side chain (couple step) and in the pair step they underwent ring closure through a transition-metal catalysed [2+2+2] cyclotrimerisation of alkynes or nitriles using MAOS.

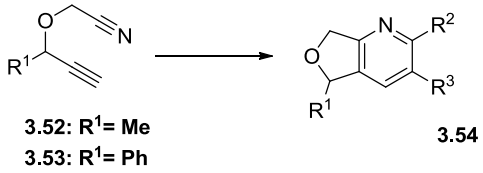


Scheme 81

Silylation of alkynenitriles **3.47** was also planned in order for further derivatisation (1 step) of the bicyclic compounds afforded in the pair step (Scheme 81). In this way, more skeletal and stereo-diversity is added to the library of compounds.

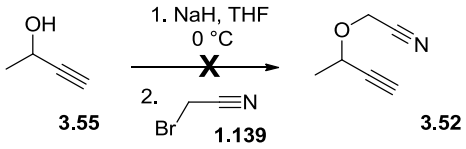
3.3 Preparation of [2+2+2] substrates: Build and Couple steps

3.3.1 Oxygen containing compounds



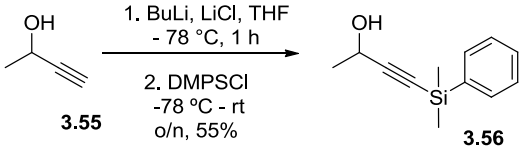
Scheme 82

The target molecules are alkynenitriles **3.52/3.53** which will afford dihydrofuropyridine derivatives **3.54** after the pair step (Scheme 82).



Scheme 83

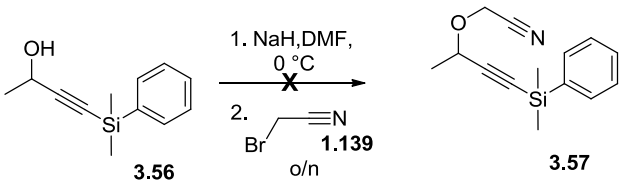
Synthesis of alkynenitrile **3.52** was attempted through the reaction of but-3-yn-2-ol **3.55** with sodium hydride and bromoacetonitrile **1.139** (Scheme 83). Bromoacetonitrile **1.139** had to be used in a large excess (10 eq.) to drive the reaction to completion. Unfortunately, due to issues of volatility, the product **3.52** could not be separated from the excess of bromoacetonitrile **1.139**, even after normal and fractional distillations were carried out.



Scheme 84

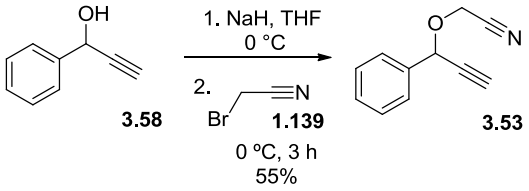
Addition of a silyl group to the terminal alkyne would overcome the volatility issue and fulfil the objectives (section 1.6) of allowing for subsequent derivatisation after ring closure to increase the diversity of the library. The selective silylation of the terminal alkyne was carried out with dimethylphenylsilyl chloride (DMPSCl) in the presence of LiCl (Scheme 84) and the desired product **3.56** was obtained in 55% yield.[157] LiCl coordinates with the oxygen anion that is formed by the reaction of BuLi with the alcohol group, thus

preventing it from reacting with DMPSCl. The low yield of the product may result from an inefficient coordination with LiCl; a less polar compound was observed by TLC but not isolated, consistent with formation of the bis-silylated compound.



Scheme 85

Alkylation of silylalkyne **3.56** with sodium hydride and bromoacetonitrile **1.139** was not possible (Scheme 85); all attempts using different amounts of both base and alkylating agent led to decomposition of the reaction mixture. Slightly weaker bases such as lithium hexamethyldisilazane (LHMDS), sodiumhexamethyldisilazane (NaHMDS) and ^{t}BuOK or a different protecting group such as TBDMS, which is more stable towards basic conditions, could have been employed.

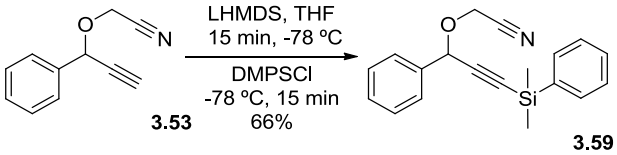


Scheme 86

Entry	Base (eq.)	Solvent	Temperature	% yield 3.53
1	NaH (4.4)	THF	0 ºC → - 20 ºC → 0ºC	55
2	NaHMDS (1.1)	THF	0 ºC – rt	34
3	NaHMDS[a] (1.1)	THF	-78 ºC – 0 ºC	Degradation
4	^{t}BuOK (1.1)	THF	0 ºC - rt	Degradation
5	NaH (4.4)	DMF	0 ºC → -20 ºC → 0 ºC	Degradation

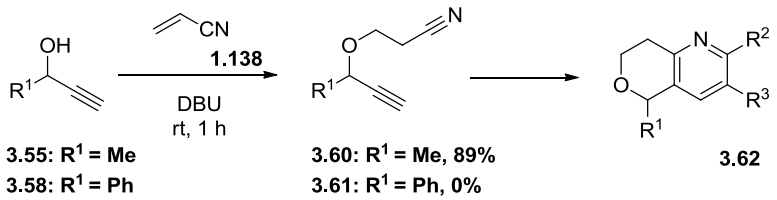
Table XX – Optimisation of alkylation of alcohol 3.58 with bromoacetonitrile 1.139. [a]Addition of NaHMDS to a solution of alcohol and bromoacetonitrile at -78 ºC.

Due to all the problems reported above, it was decided to change the starting building block to 1-phenylprop-2-yn-1-ol **3.58** which is not a volatile substrate. Alkylation of this compound was initially carried out with sodium hydride and bromoacetonitrile **1.139** (Scheme 86, Table XX, entry 1) yielding 55% of product **3.53**. Other bases and reaction conditions were investigated but it was not possible to improve on the original result.



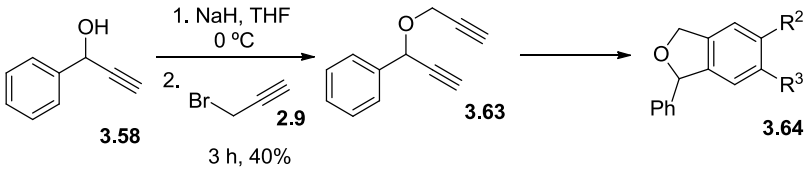
Scheme 87

Compound **3.53** was silylated with DMPSCl in the presence of LHMDS affording the desired product **3.59** in 66% yield (Scheme 87).[158]



Scheme 88

In order to synthesise substrates leading to dihydropyranopyridine derivatives **3.62** alkylation of but-3-yn-2-ol **3.55** with acrylonitrile **1.138** was carried out in the presence of substoichiometric 1,8-diazabicycloundec-7-ene (DBU) affording the desired alkynenitrile **3.60** in 89% yield (Scheme 88).[159] When the same reaction conditions were applied to 1-phenylprop-2-yn-1-ol **3.58** the reaction mixture became an insoluble resin, regardless of the reaction temperature or mode of acrylonitrile addition. These observations suggest that polymerisation of the acrylonitrile is taking place, however it is not clear at present why polymerisation does not happen when but-3-yn-2-ol **3.55** is used.



Scheme 89

Entry	Solvent	Temperature (ºC)	Time (h)	Yield 3.63 (%)
1	THF	0	3	40
2	Et_2O	0 - rt	o/n	40
3	Et_2O	reflux	o/n	45
4	DMF	0 - rt	3	25

Table XXI – Attempts to optimise the alkylation of alcohol 3.58 with propargyl bromide 2.9.

It was decided to compare the reactivity of the transition-metal catalysed [2+2+2] cyclotrimerisations of tethered alkynenitrile substrates **3.52** and **3.60** with a simple tethered diyne **3.63** which would form dihydroisobenzofuran derivatives **3.64** (Scheme 89), further contributing to the diversity of the small library. The building block **3.63** was obtained in 40% yield from the reaction of 1-phenylprop-2-yn-1-ol **3.58** with sodium hydride and propargyl bromide **2.9** (Scheme 89). Despite several attempts to optimise the reaction conditions (Table XXI), none of the modifications were successful in achieving a better yield.

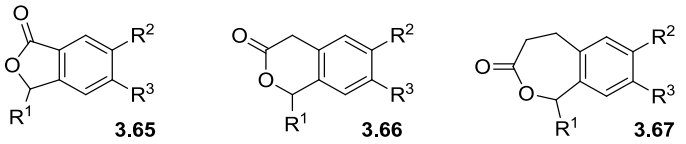
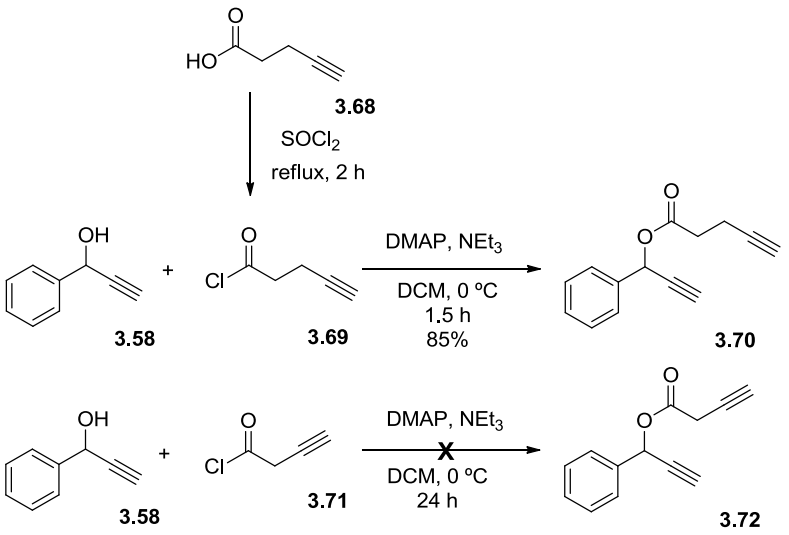


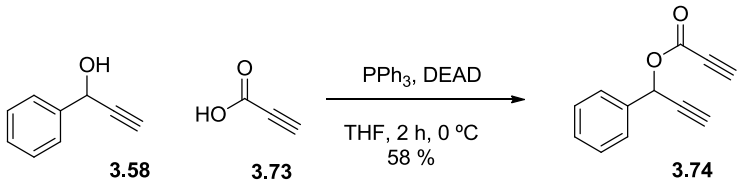
Figure 20 – Isobenzofuranone, isochromanone and dihydrobenzoxepinone.

The last strategy to introduce diversity in the oxygen containing bicycles was to incorporate a carbonyl group to the non-aromatic ring, in order to afford isobenzofuranone **3.65**, isochromanone **3.66** and dihydrobenzoxepinone **3.67** derivatives (Figure 20).



Scheme 90

The parent esters were planned to be synthesised by reaction of alcohol **3.58** with the acyl chloride. Accordingly, pent-4-ynoyl chloride **3.69** (generated *in situ* from the reaction of the corresponding acid **3.68** in refluxing thionyl chloride)[160] was reacted with 1-phenylprop-2-yn-1-ol **3.58** in the presence of DMAP and NEt_3, affording the desired ester **3.70** in 85% yield (Scheme 90).[161] Next, the esterification was attempted with but-3-ynoyl chloride **3.71** (Scheme 90). Unfortunately, no reaction occurred when alcohol **3.58** was treated with acyl chloride **3.71** under identical reaction conditions. Thinking that the problem could have been the formation of the acyl chloride **3.71**, the reaction was repeated using oxalyl chloride in DMF/DCM at rt,[162] but again no reaction was observed. A Mitsunobu reaction was also attempted but the reaction conditions caused degradation of the reaction mixture.



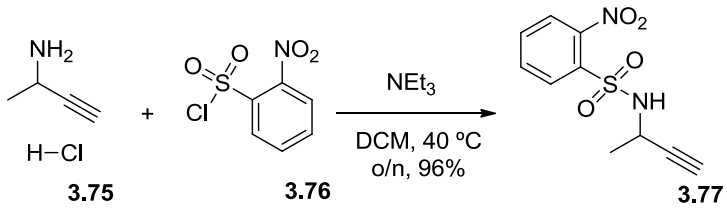
Scheme 91

Entry	Reactions conditions	%Yield 3.74
1	Propiolic acid chloride, DMAP, NEt_3, DCM	Did not react
2	EDCI, DMAP, NEt_3, DCM, -78 ºC, 5 h	24
3	PPh_3, DEAD, THF, 0 ºC, 2 h	58

Table XXII – Attempts on the esterification of alcohol 3.58.

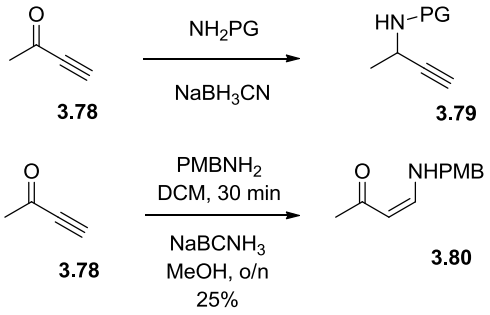
1-Phenylprop-2-yn-1-ol **3.58** did not react with propiolic acid chloride, in the presence of DMAP and NEt_3. Employing peptide coupling conditions (EDCI, DMAP and NEt_3, Table XXII, entry 2) the desired product was obtained with a low yield (24%). Mitsunobu reaction gave ester **3.74** in reasonable yield (58%)[163]

3.3.2 Nitrogen containing compounds



Scheme 92

The next point to introduce diversity to the library was to incorporate nitrogen containing compounds at the build stage. But-3-yn-2-amine hydrochloride **3.75** can be protected as the nosylate in high yield (Scheme 92). Unfortunately, this required building block **3.75** is scarce and due to its lack of availability it was necessary to synthesise it.

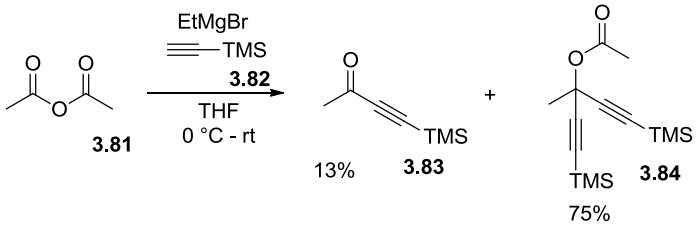


Scheme 93

Entry	Amine	Acid	Solvent	Reducing agent	% yield	
					3.79	3.80
1	NH_2Ns	Acetic acid	MeOH/THF	$NaBH_3CN$	Degradation	
2	NH_2PMB	---	MeOH	$NaBH_3CN$	---	25
3	NH_2Ns	TfOH	Nitromethane	Et_3SiH	Degradation	
4	NH_2PMB	TfOH	Nitromethane	Et_3SiH	---	[a]

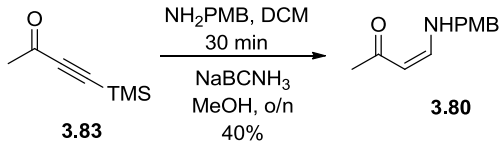
Table XXIII – Attempted reductive amination of ketone 3.78. [a] observed but not quantified

The simplest way to obtain nosyl-protected amide **3.77** would be through a reductive amination of commercially available but-3-yn-2-one **3.78** (Scheme 93). When the reductive amination was attempted with nosyl amine and sodium cyanoborohydride in the presence of a stoichiometric quantity of acetic acid,[164] the reaction mixture decomposed (Table XXIII, entry 1). Changing the amine to *p*-methoxy benzyl (PMB) amine, afforded alkene **3.80** instead of the desired amide **3.79** (entry 2, Scheme 93). Based on the ^{1}H NMR coupling constant (*J* 7.4 Hz) it can be concluded that alkene **3.80** is in the *cis* conformation. Similar results were obtained when triethylsilane was used as the reducing agent (entry 3, 4). Since the initial attack on the ketone by the amine is readily reversible, it is likely that the reaction fails due to inability to form the intermediate imine, and the small amount of **3.80** formed is the product of a non-reversible side reaction.



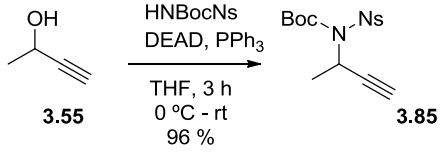
Scheme 94

Attack on the terminal alkyne could be prevented by the presence of a protecting group. Therefore, ketone **3.83** was prepared through the reaction of acetic anhydride **3.81** and ((trimethylsilyl)ethynyl)magnesium bromide generated *in situ* (Scheme 94). This reaction has been reported to afford **3.83** in 75% yield.[165] Surprisingly, product **3.83** was obtained in 13% yield, with 3-methyl-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl acetate **3.84** as the major product (75%). This by-product is formed from a second addition of the Grignard reagent to the carbonyl of product **3.83**, followed by reaction of the resulting anion with acetic anhydride. In an attempt to avoid the formation of by-product **3.84**, the order of the addition of the reagents during the course of the reaction were swapped; therefore the freshly formed Grignard was added dropwise into the acetic anhydride to avoid the presence of excess Grignard as the ketone formed. The yield did not increase, in spite of the low yields it was decided to continue the synthesis.



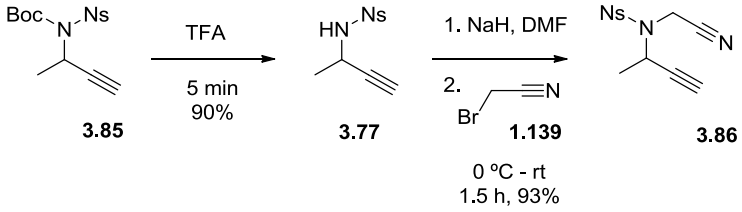
Scheme 95

The reductive amination was then accomplished by treating the TMS-protected ketone **3.83** and PMB amine with $NaBH_3CN$ (Scheme 95). The TMS group was sensitive to the reaction conditions and again alkene **3.80** was obtained. There are other alternatives described in the literature for the synthesis of the TMS-protected ketone **3.83** that could have been employed to improve the yield of the product formed, for example: reaction of acetyl chloride either with BTMSA in the presence of aluminium trichloride[166] or with TMS-acetylene in the presence of zinc chloride and ^{n}BuLi[167] or an oxidation of 4-trimethylsilyl-3-butyn-2-ol with manganese.[168] However, due to the instability of the TMS group towards the reductive amination, this approach was not further explored.



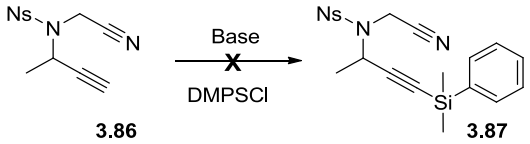
Scheme 96

An alternative to the reductive amination for the synthesis of protected amide **3.77** is a Mitsunobu reaction on but-3-yn-2-ol **3.55**. Therefore, but-3-yn-2-ol **3.55** was reacted with *N,N*-Boc-nosyl amine in the presence of diethyl azodicarboxylate (DEAD) and PPh_3 in THF, affording the diprotected amide **3.85** in 96% yield (Scheme 96).[169] Nosyl amine itself was also used for the Mitsunobu reaction, however a much lower yield was obtained (38%).



Scheme 97

N,N-Boc-nosyl amine **3.85** was deprotected with TFA, yielding the desired amine **3.77** in 90% yield (Scheme 97). Alkylation with sodium hydride and bromoacetonitrile **1.139** in DMF afforded alkynenitrile **3.86** in 93% yield (Scheme 97).



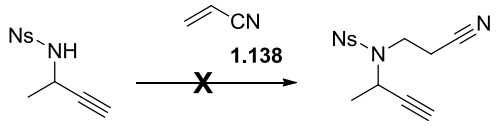
3.86 **3.87**

Scheme 98

Entry	Base (eq.)	Solvent	Temperature	% yield 3.87
1	^{n}BuLi (1.5)	THF	-78 ºC	Degradation
2	LDA (1.2)	THF	-78 ºC	Degradation
3	LHMDS (1.05)	THF	-78 ºC	Degradation
4	NaHMDS (1.05)	THF	-78 ºC	Degradation
5	EtMgBr (1.1)	THF	0 ºC	---[a]

Table XXIV – Reactions conditions attempted for the silylation of alkynenitrile 3.86. [a] Isolated fractions were mixtures.

Next, it was decided to silylate the terminal alkyne as previously done for the parent oxygen compound **3.53** (Scheme 98). Several reactions of the tethered alkynenitrile **3.86** with DMPSCl in the presence of different bases were attempted, but none were successful (Table XXIV); all the attempts led to decomposition of the reaction mixture, even though very low temperatures were used, preventing the synthesis of compound **3.87**.



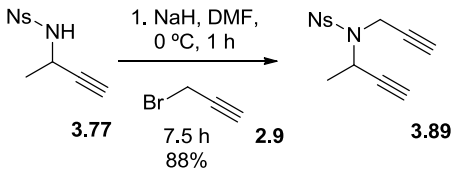
3.77 **3.88**

Scheme 99

Entry	NaH	DBU	NEt_3	% yield 3.88
1[a]	✓	---	---	---
2[a]	---	✓	---	---
3[b]	---	✓	✓	---

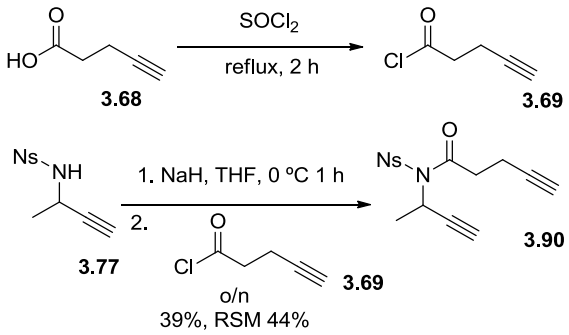
Table XXV –Attempted alkylation of amide 3.77 with acrylonitrile 1.138. [a] rt, [b] 60 ºC.

Several attempts were also made towards the alkylation of amide **3.77** with acrylonitrile **1.138** (Scheme 99, Table XXV). However, as with compound **3.58** the reaction afforded an insoluble yellow precipitate, therefore it was also not possible to synthesise the desired alkynenitrile **3.88**.



Scheme 100

Dialkyne **3.89** was synthesised in a good yield from the reaction of amide **3.77** with sodium hydride and propargyl bromide **2.9** (Scheme 100).



Scheme 101

Entry	Base	Solvent	Time (h)	Temperature	Coupling agent	Ratio 3.77:3.90
1[a]	NaH	THF	o/n	rt	---	1:1.1[d]
2[b]	NaH	DMF	o/n	rt	---	1:0.6[e]
3[b]	NaH	DMF	o/n	60 ºC	---	2.3:1[e]
4[c]	NaH	DMF	9	rt	DIC	Did not react
5[c]	NEt_3	DCM	o/n	rt	PyAOP	1:1[e]

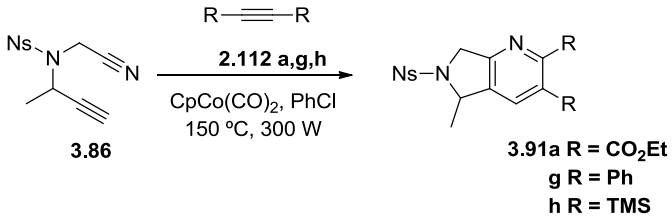
Table XXVI – Optimisation of amide 3.90 formation. [a] acyl chloride formed from pent-4-ynoic acid and thionyl chloride, 2 h, reflux, [b] acyl chloride formed from pent-4-ynoic acid and oxalyl chloride, 2 h rt, [c] Reaction with pent-4-ynoic acid, [d] isolated, [e] analysis of crude NMR.

Acylation of amide **3.77** was initially carried out with sodium hydride and pent-4-ynoyl chloride **3.69** (generated *in situ* and used immediately without further purification) in THF, affording product **3.90** in 39% yield with 44% RSM **3.77**

(Scheme 101, Table XXVI, entry 1). Despite several attempts to improve the yield of **3.90** (Table XXVI), it was impossible to drive the reaction to completion and both **3.77** and **3.90** had the same R_f, which made their separation very difficult.

3.4 Pair step: transition-metal catalysed [2+2+2] cyclotrimerisations of alkynes and nitriles

3.4.1 Napthyridine derivatives

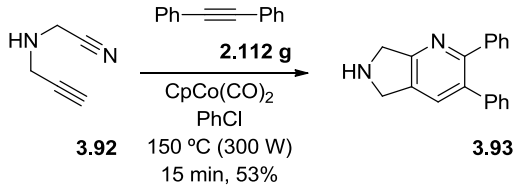


Scheme 102

Entry	Catalyst[a]	T /power	Time (min)[b]	Sol.	Mono alkyne (eq.)	% 3.86	% 3.91
1	$CpCo(CO)_2$	150 °C, 300 W	30	PhCl	**2.112g** (3.5)	83	9
2	$CpCo(CO)_2$	300 W max (93 °C)	25	PhCl	**2.112g** (3.5)	Did not react	
3	$CpCo(CO)_2$	150 °C, 300 W	45	PhMe	**2.112g** (10)	54	11
4	$CpCo(CO)_2$	150 °C, 300 W	30	PhMe	**2.112h** (10)	Did not react	
5	Cp*Ru(cod)Cl	150 °C, 300 W	15	PhCl	**2.112g** (3.5)	[c]	
6	Cp*Ru(cod)Cl	150 °C, 300 W	15	PhCl	**2.112a** (10)	[c]	
7	Cp*Ru(cod)Cl	rt	240	PhCl	---	[c]	
8	$Ni(CO)_2(PPh_3)_2$	150 °C, 300 W	30	PhCl	**2.112g** (3.5)	Did not react	
9	$Ni(CO)_2(PPh_3)_2$	300 W max (62 ºC)	30	PhMe	**2.112g** (10)	Did not react	
10	$Cl_2Pd(PPh_3)_2$	120 °C, 300 W	20	PhMe	**2.112g** (10)	Did not react	
11	$ClRh(PPh_3)_3$	150 °C, 300 W	15	PhCl	**2.112g** (10)	Degradation	
12	Grubbs' I	150 °C, 300 W	30	PhCl	**2.112g** (3.5)	Degradation	

Table XXVII – Optimisation of the cyclotrimerisation of alkynenitrile 3.86. [a] catalyst (20 mol %), [b] total reaction time, reactions were done in cycles of 15 minutes in a closed vessel, [c] mixture of unidentifiable compounds.

The work began by following the reaction conditions described by Zhou and co-workers for the synthesis of naphthyridines;[170] alkynenitrile **3.86** was reacted with diphenylacetylene **2.112g** (3.5 eq.) in chlorobenzene (PhCl) catalysed by $CpCo(CO)_2$ (20 mol %). The reaction was performed under microwave irradiation in a closed vessel at 150 ºC (300 W) for 30 minutes (15 + 15 minutes) (Scheme 102, Table XXVII, entry 1). When MAOS is used there are two factors that cannot be controlled at the same time: the power and the temperature. For example, this reaction was set up to 150 ºC employing a maximum power of 300 W, i.e., the microwave would give the system the maximum power of 300 W in order to achieve 150 ºC as quickly as possible, afterwards the power would oscillate between 50-150 W in order to maintain that temperature. Alternatively, the microwave can be set to deliver a fixed power throughout the reaction; depending on the power level set and on the reaction conditions, mainly the solvent (see section 3.2) the system will reach a constant temperature. With the reaction conditions reported by Zhou and co-workers the desired product **3.91g** was isolated in 9% yield. At first, the reaction was performed for 15 minutes and after checking that it was not complete it was irradiated for a further 15 minutes after which no difference in the SM/P ratio was observed (entry 1).



Scheme 103[170]

The low yield of the product **3.91g** obtained was very disappointing, because the literature describes a very similar reaction in very good yield, with the same catalyst and same monoalkyne **2.112g** (Scheme 103).[170] Consequently, alkynenitrile **3.86** was deprotected and it was subjected to the same reaction conditions and after 15 minutes no reaction had occurred, after two more irradiation cycles (15 minutes each) the reaction mixture degraded. Comparing both the deprotected **3.86** and the examples described in the literature **3.93**,[170] it was not expected that the presence of the methyl group would make such a

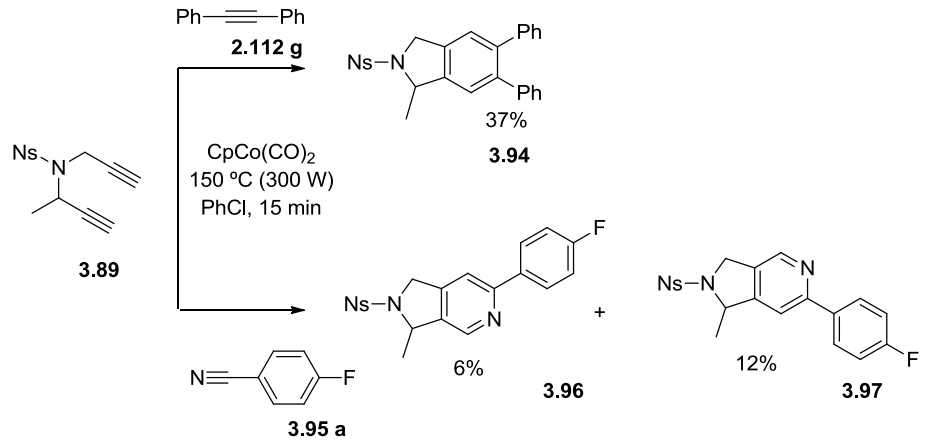
big difference. Therefore, optimisation of the reaction conditions was carried out (Table XXVII, Scheme 102).

It was decided to apply the maximum power of the microwave (300 W) in the next attempt (entry 2). The microwave used has a specific option that allows it to apply the maximum power of 300 W whilst the system is simultaneously cooled with a nitrogen stream, in this way only a certain temperature was achieved (in this case 93 ºC). Unfortunately, no product was formed. Increasing the quantity of monoalkyne to 10 eq., while performing the reaction in toluene (entry 3) at 150 ºC, did not increase product yield. A smaller amount of RSM was observed compared to entry 1, but that might be due its decomposition under the increased reaction pressure (entry 3).

Cp*Ru(cod)Cl was the next catalyst used for the [2+2+2] cyclotrimerisation, because it was the one that afforded the best results in the previous chapter (section 2.2.1). The conditions used were 150 ºC (300 W) either with diphenylacetylene **2.112g** or diethylacetylene dicarboxylate **2.112a** (entries 5 and 6) affording the same mixture of compounds. Obtaining the same by-product from reactions of two different monoalkynes suggested that the product resulted from the Ru-catalysed reaction of the alkynenitrile **3.86** alone. It might be the case that this catalyst is not chemoselective enough to coordinate with alkynenitrile **3.86** and prefers to catalyse its oligotrimerisation. Treatment of alkynenitrile **3.86** with the catalyst at room temperature yielded the same unidentified mixture of compounds, which could be proven by ^{1}H NMR spectrum comparison (entry 7). Other catalysts were also used (entries 8-12) with similar lack of success.

In these reactions only toluene and chlorobenzene were used. These are the most common solvents used in [2+2+2] cyclotrimerisations and they are also weak microwave absorbers (Table XVIII, section 3.2); the aim here was to use a weakly absorbent solvent to try to get the maximum power output from the microwave. If a highly absorbing solvent was chosen like ethanol, the reaction system would reach 150 ºC very quickly and then the microwave only needs to give a small amount of power to maintain that temperature, minimising the exposure of the reaction mixture to the radiation. Once the system reached the set temperature the power oscillated between 50-150 W, and during the complete reaction time the system was subjected to the radiation.

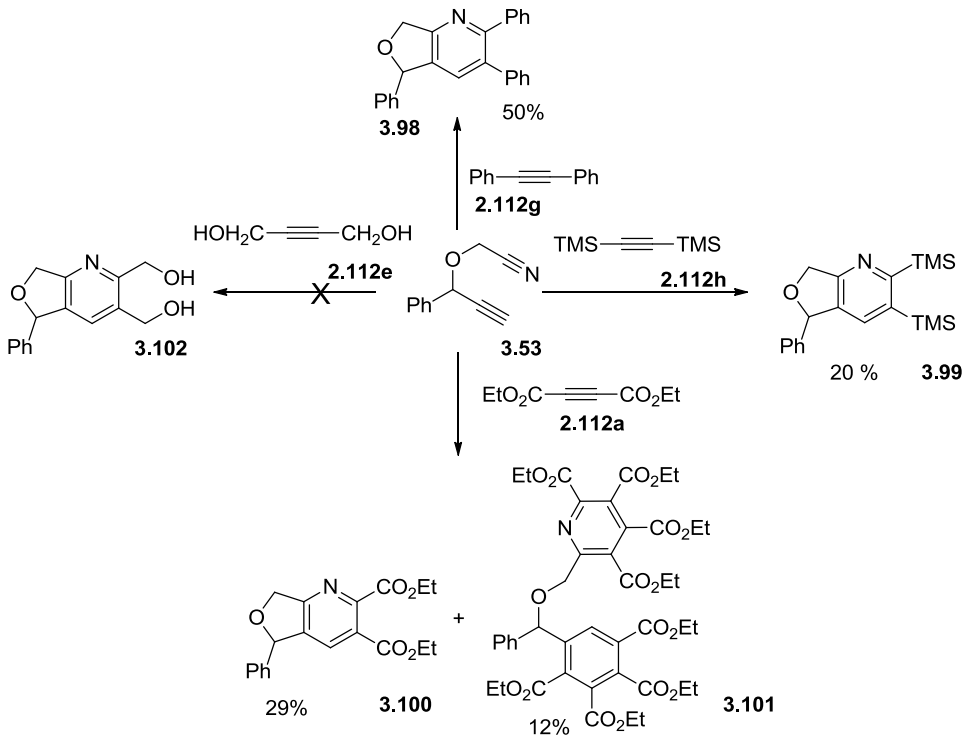
3.4.2 Isoindoline derivatives



Scheme 104

Dialkyne **3.89** was reacted with diphenylacetylene **2.112g** and 4-fluorobenzonitrile **3.95a** under the best conditions obtained above, $CpCo(CO)_2$ in chlorobenzene at 150 ºC (300 W) for 15 minutes (Scheme 104), affording the respective cyclic products in low % yield.

3.4.3 Dihydrofuro[3,4-b]pyridine derivatives



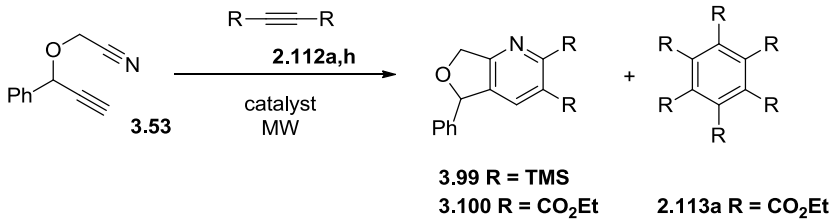
Scheme 105

Entry	T /power	Time[a] (min)	Solvent	Monoalkyne (eq.)	Product: yield
1	150 ºC, 300 W	30	PhCl	**2.112g** (10)	**3.98**: 50% **3.53**: 17%
2	150 ºC, 300 W	15	PhCl	**2.112h** (10)	**3.99**:20%
3	150 ºC, 300 W	15	PhCl	**2.112a** (10)	**3.100**: 29% **3.101**:12%
4	Open vessel 120 ºC, 300 W	30	PhMe	**2.112a** (10)	Did not react
5	Reflux	60	PhMe	**2.112a** (10)	**3.100**: 15%
6	150 ºC, 300 W	30	PhCl	**2.112e** (10)	Did not react

Table XXVIII – [2+2+2] cyclotrimerisation of alkynenitrile 3.53 with different monoynes (2.112a,e,g,h) catalysed by $CpCo(CO)_2$ (20 mol %). Unless otherwise mentioned the reactions were done in a closed vessel. [a] total time, reactions were done in cycles of 15 minutes.

The focus was then turned to the synthesis of dihydrofuropyridine derivatives. When alkynenitrile **3.53** was reacted with diphenylacetylene **2.112g** (10 eq.) and $CpCo(CO)_2$ (20 mol %) at 150 ºC (300 W) in a closed vessel the desired cyclic product **3.98** was obtained in 50% yield along with 17% RSM **3.53** (Scheme 105, Table XXVIII, entry 1). With this encouraging result some other monoalkynes were used in the cyclotrimerisation (Scheme 105 and Table XXVIII). Reaction with BTMSA **2.112h** afforded cyclic product **3.99** in 20% yield along with decomposition of the reaction mixture (entry 2). When alkynenitrile **3.53** was reacted with diethylacetylene dicarboxylate **2.112a** (entry 3), after 15 minutes the reaction was complete affording product **3.100** (29%) along with by-product **3.101** (12 %). By-product **3.101** results from the reaction of two molecules of diethylacetylene dicarboxylate on both branches of the alkyne and nitrile. The reaction was then repeated, using open vessel conditions to see if the formation of the by-product **3.101** would be suppressed (entry 4). This meant that the reaction vessel was set up with a condenser and the temperature of the reaction would not go beyond the boiling point of the solvent, which also allowed the monoalkyne to be added dropwise. However, no product was formed under these conditions (not observed by ultra performance liquid chromatography (UPLC)). The reaction in refluxing toluene was complete after 1 h and afforded only 15% of product **3.100** along with **2.113a** and by-product **3.101** which were not quantified (entry 5). There was no reaction when 1,4-

butynediol **2.112e** was used as the monoalkyne (entry 6), which might be associated with poor solubility of 1,4-butynediol **2.112e** in the reaction solvent. The solubility issue might have been overcome with a small addition of ethanol for example using a solvent system of toluene/ethanol 4:1.



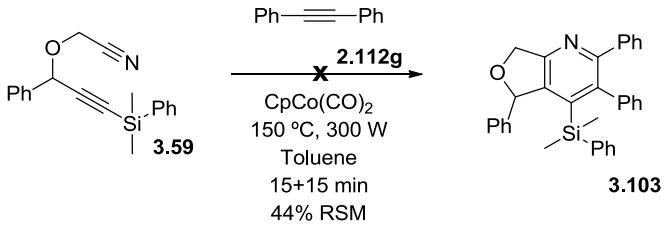
Scheme 106

Entry	Catalyst (mol %)	T /power	Time (min)	Solvent	Monoalkyne (eq.)	Products
1	Cp*Ru(cod)Cl (10)	150 ºC 300 W	5	PhCl	**2.112a** (10)	**2 .113a**
2	Cp*Ru(cod)Cl (10)	150 ºC 300 W	5	PhMe	**2.112a** (10)	**2.113a**
3	$Co(CO)_8$ (20)	150 ºC 300 W	30	PhCl	**2.112a** (10)	Did not react
4	$Ni(CO)_2(PPh_3)_2$ (20)	120 ºC 300 W	30	PhMe	**2.112h** (10)	Degradation

Table XXIX – [2+2+2] cyclotrimerisation of alkynenitrile 3.53 with diethylacetylene dicarboxylate 2.112a and BTMSA 2.112h.

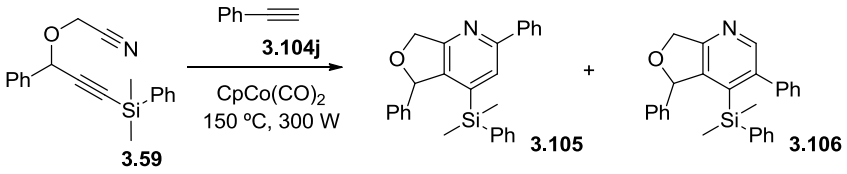
Two more catalysts were tested for the reaction of alkynenitrile **3.53** and diethylacetylene dicarboxylate **2.112a**: $Co(CO)_8$ (20 mol %) and Cp*Ru(cod)Cl (10 mol %) (Scheme 106, Table XXIX). When $Co(CO)_8$ was used no reaction happened (entry 3) but when Cp*Ru(cod)Cl was used in either chlorobenzene (150 ºC, 300 W, entry 1) or toluene (120 ºC, 300 W, entry 2) the entire reagent was consumed after 5 minutes, affording only homotrimerised product **2.113a**. In contrast to alkynenitrile **3.86** (Scheme 102, Table XXVII) alkynenitrile **3.53** tended to degrade, with no formation of a major compound more polar than the starting material. This evidence one more time reinforces the fact that this catalyst might not be chemoselective for [2+2+2] cyclotrimerisation of alkynenitrile **3.53** and a monoalkyne, and instead might afford only oligomerisation of **3.53**.

Until this point of the work, the highest yields were achieved using $CpCo(CO)_2$ as the catalyst at 150 ºC (300 W) in chlorobenezene. Unless otherwise noted, the [2+2+2] cyclotrimerisation of alkynes discussed in the following section, were carried out under these conditions.



Scheme 107

Next, attention was turned towards cyclotrimerisation of silylated compound **3.59**, which was reacted with diphenylacetylene **2.112g** (150 ºC, 300 W, 20 mol % $CpCo(CO)_2$) (Scheme 107), however most of the starting material did not react (44% RSM). Isolated fractions only revealed aromatic peaks in the ^1H NMR spectrum and no product was observed by UPLC of the crude reaction mixture. The lack of reactivity of SM **3.59** may be explained by a steric clash between the DMPS group and the phenyl group on the monoalkyne.



Scheme 108

Entry[a]	Monoalkyne 3.104j (eq.)	Concentration of reaction mixture (M)	Ratio 3.59:3.105
1	10	0.18	1:0.06
2	10	0.36	[b]
3	10	0.09	[b]
4	10	0.018	[b]
5	10	0.005	[b]
6	10	0.0025	[b]
7[c]	---	0.18	---
8[d]	---	0.18	---[e]
9[d]	10	0.18	[b]

10	0.5	0.18	1.5:1[f]
11	1	0.18	2.6:1[f]
12	3	0.18	1.4:1[f]

Table XXX – Optimisation of the reaction of silylated alkyne 3.59 and phenylacetylene 3.104j. [a] All reactions were carried out with 20 mol % of $CpCo(CO)_2$ in PhCl at 150 ºC (300 W) for 30 minutes total reaction time (2 × 15 minute cycles) [b] crude ^{1}H NMR analysis: compounds present but ratio not determined. [c] $CpCo(CO)_2$ omitted. [d] Irradiation for 15 min followed by addition of diethylacetylene dicarboxylate **2.112a** (5 eq.), irradiation for more 15 min, [e] **2.113a** observed, [f] ratio determined by ^{1}H NMR analysis of the crude.

Phenylacetylene **3.104j** should bind the catalyst in an orientation to avoid the steric clash. For that reason, the reaction of silylated alkyne **3.59** with phenylacetylene **3.104j** was investigated (Scheme 108, Table XXX), in order to see if the addition would happen and if it would be regioselective.

The reaction afforded the desired product **3.105** in 3.5% (isolated yield, entry 1) with selectivity for one isomer. Along with the small amount of product **3.105**, 9 other fractions were isolated, this included 54% of RSM **3.59**. Unfortunately, all the fractions isolated were mixtures of products and no conclusion could be drawn to explain the course of the reaction.

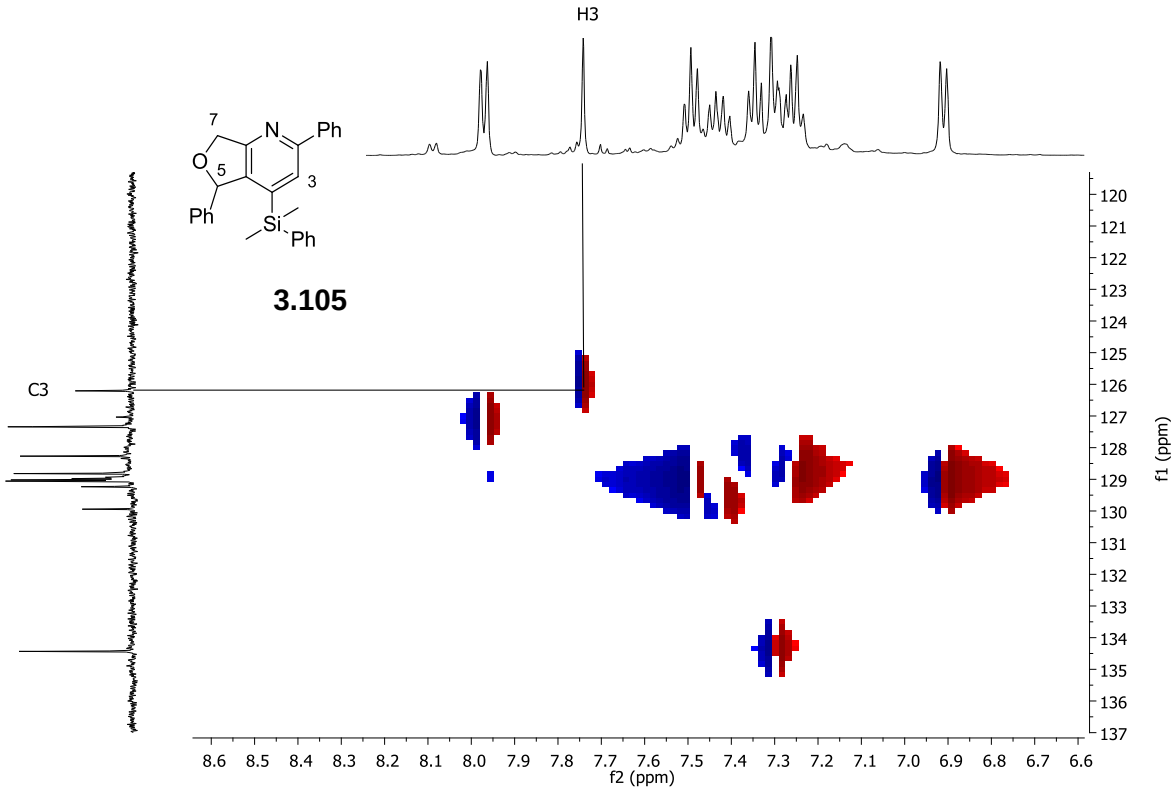


Figure 21 – HSQC spectrum of compound 3.105.

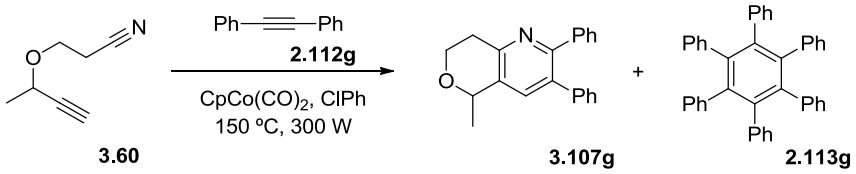
The formation of predominantly one isomer was confirmed by ^{1}H NMR spectrum where only one aromatic singlet is observed and by ^{13}C NMR spectrum where there is only one peak for each carbon on the molecule.The assignment of the isomer formed corresponds to compound **3.105** purely based on NMR spectra analysis. In the HSQC spectrum (Figure 21) the carbon C3 that correlates with the singlet H3 is the most shielded aromatic peak. In the other isomer **3.106**, H3 and C3 would be more deshielded because they would be next to the electronegative nitrogen atom. The concentration of the reaction (SM to solvent ratio) was varied (entries 2-6) in an attempt to decrease the amount of side products formed.

It was observed that more dilute reactions (entries 5 and 6 Table XXX) took more time (5-8 minutes respectively) to achieve the set reaction temperature of 150 ºC. For the standard concentration (0.18 M) the reaction took 1.5 minutes to reach that temperature. The desired product **3.105** was observed in all the reactions by TLC and UPLC, however all the more dilute reactions yielded a complex mixture of products (analysis by ^{1}H NMR of the crude) regardless of the concentration, apart from the reaction with the increased concentration (entry 2) which led to an increase in the amount of side products formed. It seemed that the concentration did not play an important role in controlling product distribution. Due to the observation that the ratio between SM and product did not change between the first and second irradiation (TLC observation) there were concerns about the stability of the components of the reaction mixture while irradiation was taking place. To investigate their stability, silylated alkynenitrile **3.59** was irradiated in chlorobenzene for 30 minutes (15 + 15 minutes, entry 7) and no degradation occured after each cycle. The next parameter to check was the lifetime of the catalyst. From previous experiments (section 3.4), it is known that $CpCo(CO)_2$ efficiently catalyses the trimerisation of diethylacetylene dicarboxylate **2.112a**. Accordingly, $CpCo(CO)_2$ (20 mol %) was irradiated in chlorobenzene for 15 minutes before diethylacetylene dicarboxylate **2.112a** (5 eq.) was added. After, the reaction mixture was subjected to irradiation for a further 15 minutes (entry 8). Monitoring by TLC revealed formation of the homotrimerised product **2.113a**, indicating that the catalyst was still functional in the model system. However, when silylated alkynenitrile **3.59**, phenylacetylene **3.104j** and $CpCo(CO)_2$ in chlorobenzene were irradiated for 15 minutes, followed by addition of diethylacetylene

dicarboxylate **2.112a** (5 eq.) and irradiation for a further 15 minutes (entry 9), no homotrimerised product **2.113a** formed, suggesting that in this reaction system, after 15 minutes the catalyst is dead. It is possible the catalyst was also catalysing the trimerisation of phenylacetylene **3.104j** in preference to diethylacetylene dicarboxylate **2.112a** or the desired reaction of **3.59**, therefore, the effect of the quantity of monoalkyne added to the reaction mixture was investigated. Three different quantities were chosen (0.5, 1 and 3 eq., entries 10-12). Unreacted starting material **3.59** was observed in all reactions (by UPLC), however no conclusions can be drawn in relation to the effect of increasing the quantity of monoalkyne **3.104j**.

In summary, the desired [2+2+2] reaction is regioselective, but is disfavoured compared to unidentifiable side reactions.

3.4.4 Dihydropyranopyridine derivatives



3.60 3.107g 2.113g

Scheme 109

Entry	$CpCo(CO)_2$ [a] (mol %)	Time (min)	Monoalkyne 2.112g (eq.)	% yield [b]	
				RSM	3.107g
1	20	15	10	Trace	43
2	20	15	0.5	Trace	23
3	20	15	1	Trace	42
4	20	15	3	Trace	70
5	20	30	3	Trace	56
6 [c]	20	15+15	3	---	---
7 [c]	20	10+15	3	---	---
8	20	10	3	26	56
9	10	15	3	30	46
10	10	30	3	12	55
11	100	15	3	---	76
12	10 + 10	15	3	---	62

Table XXXI – [2+2+2] cyclotrimerisation of alkynenitrile 3.60 with diphenylacetylene 2.112g. [a] Reactions in PhCl at 150 ºC (300 W), C = 0.18 M. [b] Homotrimerised product **2.58** observed but not isolated in all reactions. [c] Irradiation for

15 minutes followed by addition of diethylacetylene dicarboxylate (5 eq.) and irradiation for another 15 minutes.

Subsequently, the focus was turned towards the formation of the 6-membered ring dihydropyranopyridine derivatives.

Alkynenitrile **3.60** was reacted with diphenylacetylene **2.112g** (10 eq.) in PhCl with $CpCo(CO)_2$ (20 mol %) as the catalyst at 150 ºC (300 W), affording cyclic adduct **3.107g** in 43% yield, the remainder of the yield was the degradation products of the reaction mixture (Scheme 109, Table XXXI, entry 1).

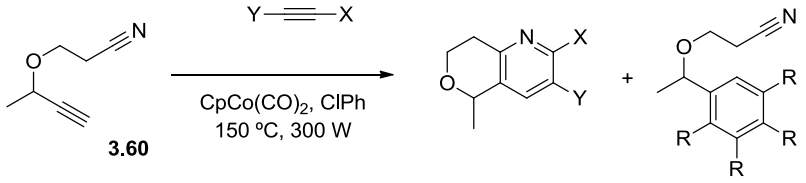
Since the reaction of alkynenitrile **3.60** with diphenylacetylene **2.112g** gave a moderate yield of the desired product **3.107g**, the conditions were further investigated in an attempt to optimise the reaction (Table XXXI). Decreasing the amount of monoalkyne from 10 to 3 equivalents (entries 2-4) increased the yield of the reaction to 70% , indicating that the homocyclisation of the monoalkyne (product **2.113g**) competes with the formation of the desired product; even when 0.5 equivalents of monoalkyne was used there was still homotrimerised product **2.113g** being formed. Extending the reaction time to 30 minutes (entry 5) decreased the amount of product formed suggesting it may be unstable to the reaction conditions.

To investigate the lifetime of the catalyst, two reactions were performed where starting material **3.60** was irradiated with diphenylacetylene **2.112g** and the catalyst for 15 and 10 minutes. After this period, diethylacetylene dicarboxylate **2.112a** was added and each solution irradiated for a further 15 minutes (entries 6 and 7). In both cases, the diethylacetylenedicarboxylate homotrimer **2.113a** was obtained, which confirmed that the catalyst was still active, in contrast to reaction of **3.59** (Scheme 108).

Decreasing the reaction time and the amount of the catalyst reduced the amount of product obtained and gave a higher percentage of RSM (entries 8-10). On the other hand increasing the amount of catalyst to a stoichiometric amount (entry 11) does not significantly increase the amount of product formed (76%).

In summary, $CpCo(CO)_2$ is not chemoselective enough to react only with the alkynenitrile **3.60**, because it competes for the homotrimerisation of diphenylacetylene **2.113g** and perhaps for the oligomerisation of the SM. The best reaction conditions found for reaction of alkynenitrile **3.60** with

diphenylacetylene (Scheme 109) are diphenylacetylene (3 eq.), 20 mol % of catalyst and irradiation of the reaction mixture over 15 minutes at 150 ºC (300 W) in chlorobenzene.

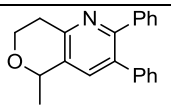
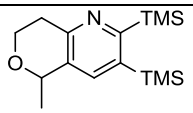
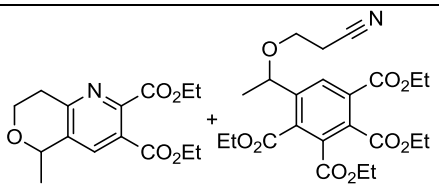
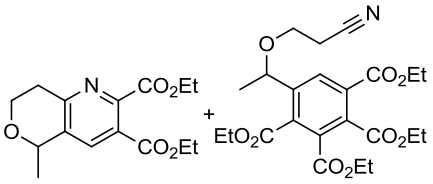
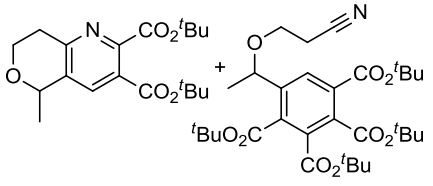


Monoalkyne
X, Y = Ph **2.112g**
X, Y = TMS **2.112h**
X, Y = CO_2Et **2.112a**
X, Y = $CO_2{}^tBu$ **2.112i**
X = Ph, Y = H **3.104j**
X = TIPS, Y = H **3.104k**
X = CH_2Br, Y = H **3.104l**
X = CH_2NH_2, Y = H **3.104m**
X = TIPS, Y = Ph **3.108n**

3.107
X, Y = Ph **3.107g**
X, Y = TMS **3.107h**
X, Y = CO_2Et **3.107a**
X, Y = $CO_2{}^tBu$ **3.107i**
X = Ph, Y = H **3.107j**
X = TIPS, Y = H **3.107k**
X = CH_2Br, Y = H **3.107l**
X = CH2NH2, Y = H **3.107m**
X = TIPS, Y = Ph **3.107n**

3.109
X, Y = CO_2Et **3.109a**
X, Y = $CO_2{}^tBu$ **3.109i**

Scheme 110

Entry	Monoalkyne	Product:yield
1	**2.112g**	 **3.107g**: 70%
2	**2.112h**	 **3.107h**: 3.5%
3 [a]	**2.112a**	 **3.107a**: 12% **3.109a**: 61%
4 [b]	**2.112a**	 **3.107a** [b] **3.109**[b]
5	**2.112i**	 **3.107i**: 16% **3.109i**: 21%

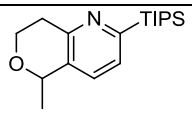
6	**3.104j**	Degradation
7	**3.104k**	 **3.107k**: 9%
8	**3.108n**	Degradation
9	**3.104l**	Did not react
10	**3.104m**	Degradation

Table XXXII – [2+2+2] cyclotrimerisation of alkynenitrile 3.60 with different monoalkynes. The reactions were carried out with 3 eq. of monoalkyne, 20 mol % of $CpCo(CO)_2$ in PhCl at 150 ºC (300 W) for 15 minutes, C = 0.18 M. [a] 5 minutes, [b] C = 0.70 μM, 10 minutes, products observed but not quantified.

The reaction of a range of monoalkynes with alkynenitrile **3.60** were investigated (Scheme 110, Table XXXII) using the previously optimised reaction conditions (Scheme 109, Table XXXI).

The reaction of alkynenitrile **3.60** with BTMSA **2.112h** (entry 2) afforded 3.5% of the desired product **3.107h**; the reaction was complete and TLC analysis suggested that the rest of the reaction mixture had degraded. The reaction with diethylacetylene dicarboxylate **2.112a** (entry 3) was completed after 5 minutes affording predominantly by-product **3.109a** (61%) along with the desired product **3.107a** (12%). Dilution of the reaction mixture to 0.70 μM, by increasing the amount of chlorobenzene added (entry 4), should in theory decrease the probability of a second molecule of monoalkyne reacting with the alkyne branch, however this was not the case; the ratio of product **3.107a**:by-product **3.109a** observed by TLC was unchanged. Another alternative to increase the yield of the desired product from the cyclotrimerisation of alkynenitrile **3.60** with a monoalkyne diester, would be to increase the steric bulk of the ester to disfavour its homotrimerisation and the by-product formation. Di-*tert*-butyl but-2-ynedioate **2.112i** was reacted with alkyenitrile **3.60** (entry 6); the reaction was complete after 15 minutes, jugdged by tlc, (was slower than with diethyl acetylenedicarboxylate **2.112a**) and afforded the desired product **3.62** in 16% yield. Unfortunately the by-product **3.109i** was also isolated although in much lower quantity (21%).

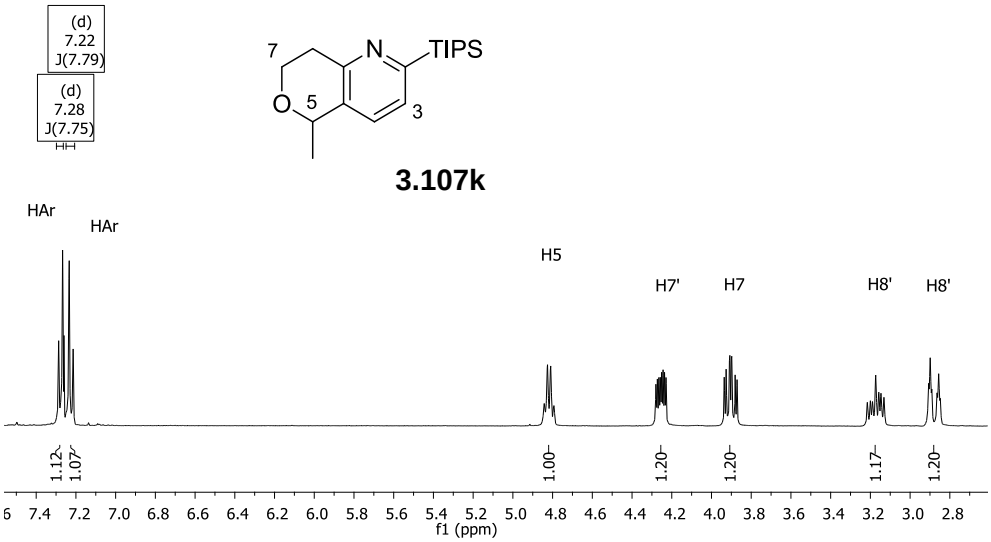
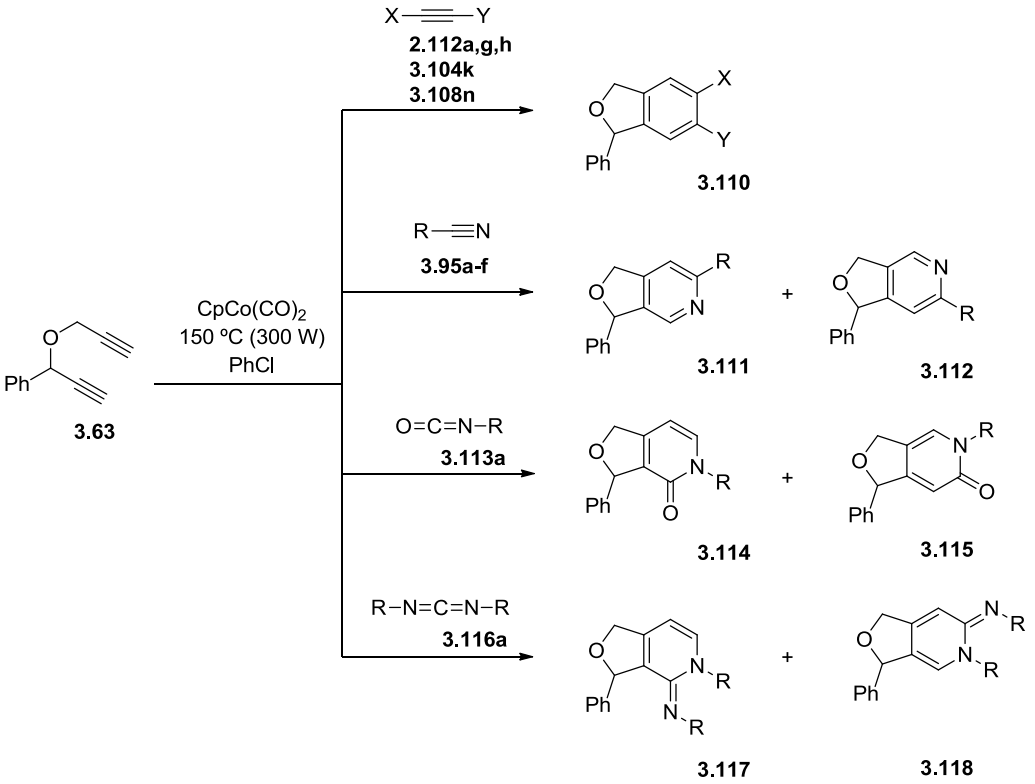


Figure 22 – ^{1}H NMR of pyranopyridine 3.107k.

TIPS acetylene afforded 9% of the desired product **3.107k** (entry 7) as a single isomer (^{13}C NMR). The ^{1}H NMR aromatic coupling constant $J_{3,4}$=7.8 Hz, characteristic of *ortho* coupling, indicates that it is structure **3.107k** (Figure 22). The product was obtained regioselectively with the bulky TIPS group placed near the nitrogen atom which is consistent with most studies with alkynenitriles and non-symmetric diyenes (section 1.4.2.2).[171,50] In contrast to the cyclotrimerisations of TIPS acetylene **3.104k** and diphenylacetylene **2.112g**, reaction with TIPS phenylacetylene **3.108n** (entry 8, Table XXXII) gave only decomposition. The reactions with propargyl bromide **3.104l** and propargyl amine **3.104m** (entries 9 and 10) did not afford any product. In the former case the reaction mixture was black, but none of the starting material reacted, while in the latter case the reaction decomposed. Propargyl bromide is seldom used in cyclotrimerisation reactions to form benzene or pyridine derivatives. However, it has been used in a thermal Diels-Alder addition to form benzene[172] and pyridine derivatives[173].

3.4.5 Dihydroisobenzofuran and dihydrofuro[3,4-c]pyridine derivatives



Alkyne
X, Y = Ph **2.112g**
X, Y = TMS **2.112h**
X, Y = CO_2Et **2.112a**
X = TIPS, Y = H **3.104k**
X = TIPS, Y = Ph **3.108n**

3.110
X, Y = Ph **3.110g**
X = TIPS, Y = H **3.110k**

Nitrile
R = 4F-Ph **3.95a**
R = Ph **3.95b**
R = 2-Py **3.95c**
R = 3-indole **3.95d**
R = 3OMe-Bn **3.95e**
R = $3CF_3$-Bn **3.95f**

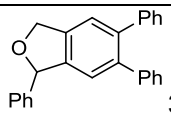
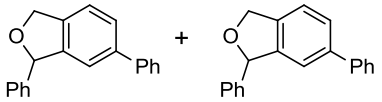
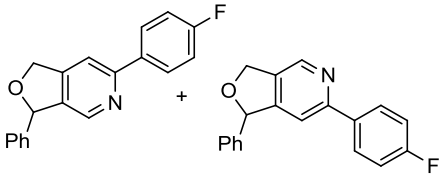
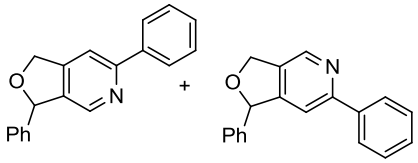
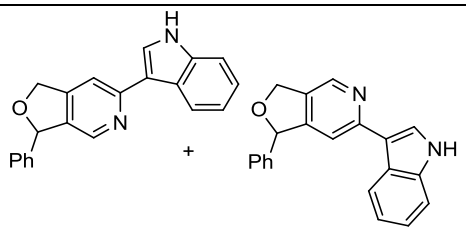
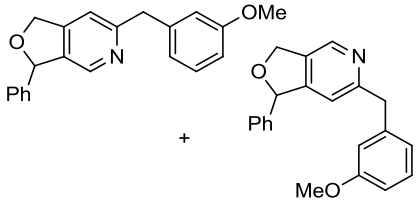
3.11
R = 4F-Ph **3.111a**
R = Ph **3.111b**
R = 3-indole **3.111d**
R = 3OMe-Bn **3.111e**

3.12
R = 4F-Ph **3.112a**
R = Ph **3.112b**
R = 3-indole **3.112d**
R = 3OMe-Bn **3.112e**
R = $3CF_3$-Bn **3.112f**

Isocyanate
R = $4CO_2EtPh$ **3.113a**

Carbodiimide
R = Cy **3.116a**

Scheme 111

Entry	Unsaturated partner (3 eq.)	Product : yield
1	**2.112g**	 **3.110g**: 97%
2	**3.108n**	Degradation
3	**2.112h**	Degradation
4	**2.112a**	Degradation
5	**3.104k**	 **3.110k** (8% 1:1 mixture of isomers)
6	**3.95a**	 **3.111a** : 31% **3.112a** : 34%
7	**3.95b**	 **3.111b** : 30% **3.112b** : 29%
8	**3.95c**	Degradation
9	**3.95d**	 **3.111d** : 20% **3.112d** : 20%
10	**3.95e**	 **3.111e** : 27% **3.112e** : 28%
11	**3.95f**	

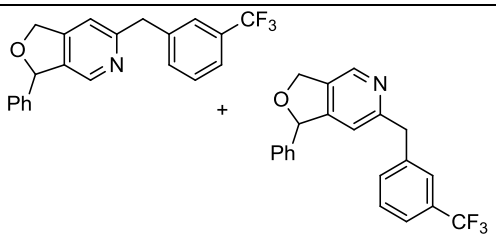
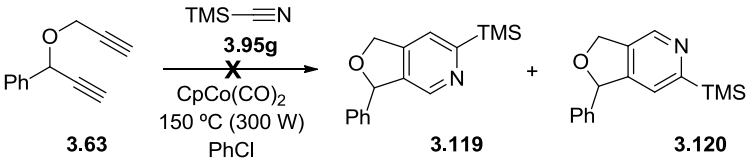
		 **3.111f** [a] **3.112f** : 28%
12	**3.113a**	Degradation
13	**3.116a**	Degradation

Table XXXIII – Reaction of dialkyne 3.63 with different partners. Reactions were catalysed by 20 mol % of $CpCo(CO)_2$ in PhCl at 150 ºC (300 W) for 15 minutes. [a] observed but could not be isolated pure.

The reaction of dialkyne **3.63** with diphenylacetylene **2.112g** in the presence of $CpCo(CO)_2$ (20 mol %) for 15 minutes afforded the desired cyclic adduct **3.110g** in 97% yield (Scheme 111 Table XXXIII, entry 1).

In order to incorporate more diversity into the final library of compounds, dialkyne **3.63** was reacted with a range of different monoalkynes and nitriles (Table XXXIII). Reacting dialkyne **3.63** with BTMSA **2.112h**, diethylacetylene dicarboxylate **2.112a** and TIPS phenylacetylene **3.108n** resulted in decomposition of the reaction mixture (entries 2-5). Reaction of dialkyne **3.63** with 4-fluorobenzonitrile **3.95a** gave two separable isomers **3.111a** (31%) and **3.112a** (34%), (entry 6). Similar results were obtained using benzonitrile **3.95b**, 2-(3-methoxyphenyl)acetonitrile **3.95e** and 2-(3-(trifluoromethyl)phenyl)acetonitrile **3.95f** (entries 7, 10, 11). Reaction with indoline-3-carbonitrile **3.95d** gave slightly lower yields of the desired products (entry 9), perhaps due to the low solubility of the indole in chlorobenzene. No regioselectivity was observed in any of the reactions of dialkyne **3.63** with the nitriles, that is because the electronics of both branches of the dialkyne are similar, so there is no electronic control of the nitrile's orientation.

Use of isocyanates and carbodiimides in the [2+2+2] cyclotrimerisation reaction would allow the synthesis of 2-pyridones and 2-iminopyridines (Section 1.4). Unfortunately, the only two cases studied here gave only decomposition of the reaction mixtures (entries 12 and 13). As potential future work, it will be important to adjust the reaction conditions for the synthesis of these two types of compounds and test different isocyanates and carbodiimides, in order to add greater diversity to the final library of compounds.



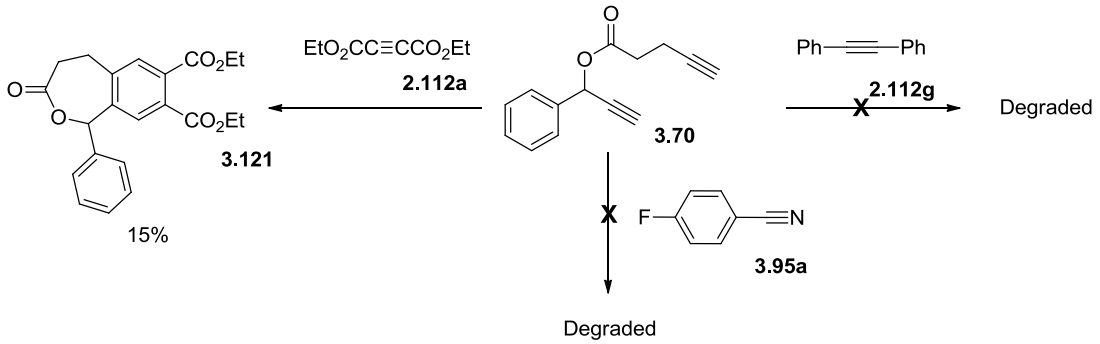
Scheme 112

Entry	Microwave[a]	Conventional heating[b]	Time (min)	K_2CO_3	Observations
1	✓	---	15	---	Degradation
2	✓	---	5	---	SM + Degradation
3	✓	---	10	---	SM + Degradation
4	✓	---	15	✓	Degradation
5	✓	---	5+5+5	✓	Degradation
6[c]	✓	---	15	✓	Degradation
7	---[b]	✓	120	✓	Degradation

Table XXXIV – Attempted cyclotrimerisation of dialkyne 3.63 with TMSCN 3.95g. Reactions were carried out with 3 eq. of TMSCN and 20 mol % of $CpCo(CO)_2$ in PhCl. [a] 150 ºC (300 W), [b] reflux, [c] 10 eq. TMSCN.

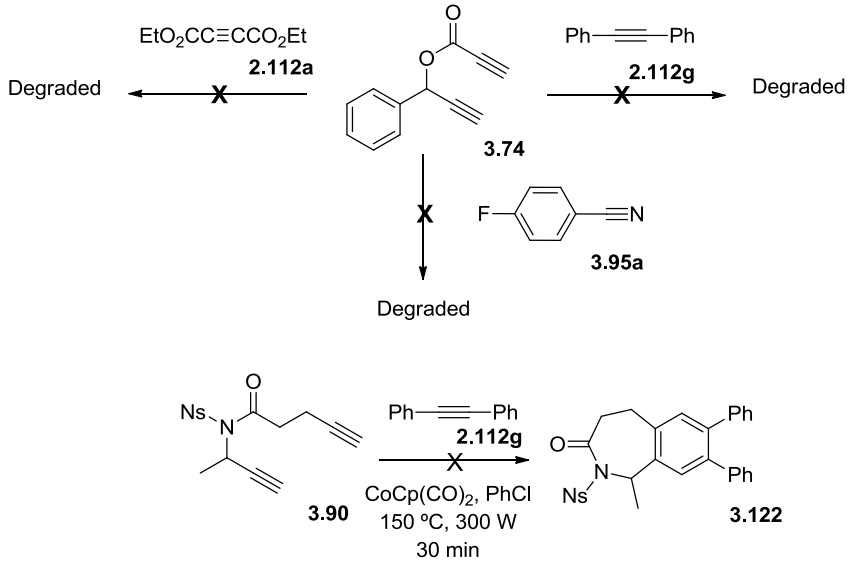
As a further attempt to install a silyl group in the cyclic product, dialkyne **3.63** was reacted with TMSCN **3.95g** (Scheme 112, Table XXXIV). Applying the previously optimised conditions, reaction of dialkyne **3.63** with TMSCN was catalysed with $CpCo(CO)_2$ in chlorobenzene at 150 ºC (300 W). After 15 minutes the reaction mixture was degraded (entry 1). Shorter reaction times (5 or 10 minutes) also gave only decomposition. It is noteworthy that there is still SM present in the reaction mixture at 10 minutes, which is completely decomposed after 15 minutes (entries 2 and 3). The degradation could be due to the release of HCN into the reaction mixture, therefore the reaction was carried out in the presence of K_2CO_3 for 15 minutes (entry 4) and also for pulses of 5 minutes until a total time of 15 minutes (entry 5). The same degradation pattern was obtained. Moreover, similar results were obtained using either 10 eq. of TMSCN **3.95g** under microwave conditions or carrying out the reaction using thermal heating (entries 6 and 7). There is no precedent for the use of TMSCN in [2+2+2] cyclotrimerisations.

3.4.6 Dihydrooxepinone, isobenzofuranone, and dihydrobenzoazepinone derivatives



Scheme 113

Reacting dialkyne ester **3.70** with diphenylacetylene **2.112g** or 4-fluorobenzonitrile **3.95a** catalysed by $CpCo(CO)_2$ at 150 ºC (300 W) under microwave irradiation (Scheme 113) led to decomposition of the reaction mixture; (very small quantities of the product were observed by UPLC). When diethylacetylene dicarboxylate **2.112a** was used as the monoalkyne, the reaction afforded product **3.121** in 15% yield.



Scheme 114

No products were obtained from reactions of dialkyne ester **3.74** with diphenylacetylene **2.112g**, diethylacetylene dicarboxylate **2.112a** or 4-fluorobenzonitrile **3.95a** (Scheme 114). The reaction of dialkyne amide **3.90** with diphenylacetylene **2.112g** was similarly unsuccessful (Scheme 114).

The building blocks derived from esters and amides seem to be more susceptible to degradation under the reaction conditions used. Future work should involve further exploration to find appropriate reaction conditions for [2+2+2] cyclotrimerisations of esters and amides.

3.5 Conclusions

The work developed showed the synthesis of heterocyclic molecules applying the concept of DOS and B/C/P strategy.

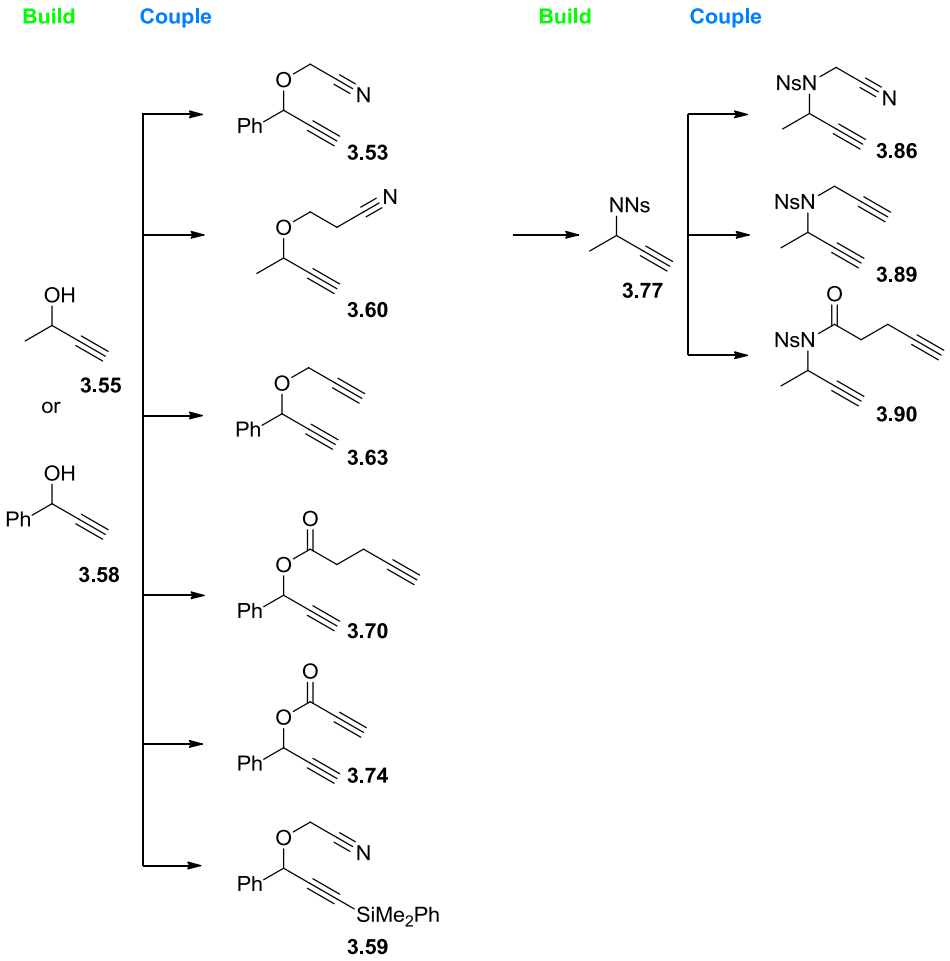


Figure 23 – Build and couple steps with oxygen and nitrogen containing compounds synthesised.

Oxygen and nitrogen containing compounds were used as building blocks for reaction with propargyl bromide **2.9**, acrylonitrile **1.138** or with an acyl chloride

in the couple step affording several products to be used in the pair step (Figure 23).

In the pair step, a microwave assisted transition-metal catalysed [2+2+2] cyclotrimerisation of tethered alkynenitriles or dialkynes was performed. The best reaction conditions found here used $CpCo(CO)_2$ as the catalyst at 150 ºC (300 W) in chlorobenzene. The transition-metal catalysed [2+2+2] cyclotrimerisations generally seem to progress with better yields with the oxygen containing compounds compared to nitrogen containing compounds, which require more work to optimise.

The work developed above illustrated the importance of MAOS in organic synthesis. Using microwave radiation it was possible to test different reaction conditions and determine and generate compounds for biological evaluation. Unfortunately, for the pair step, it is not possible to draw a good correlation between successful reactions and the electronics of the alkynenitrile, dialkyne or monoalkyne. Similarly, no conclusion can be made about the size of the non-aromatic ring formed, whether the formation of 5- or 6-membered rings is more favourable or not. Regardless of the alkyne used or ring size generated, employment of phenylacetylene led consistently to the highest yields.

It was not possible to introduce a silyl group to allow for late stage derivatisation after pairing. The oxygen-containing building block **3.53** was successfully silylated, however did not undergo cyclotrimerisation. Reaction of silylated compound **3.59** with phenylacetylene **3.104j** afforded a very small amount of product **3.105**, which was generated regioselectively with the phenyl group adjacent to the nitrogen, rather than adjacent to the sterically demanding silyl group.

Chapter 4 Biological evaluation of bi- and tricyclic compounds

4.1 General overview of cytochromes P450

The cytochrome P450s (CYPs) belong to a superfamily of haemoproteins consisting of 57 different human CYPs genes and 58 pseudogenes. CYPs are expressed mainly in the liver where they play a major role in the oxidation/metabolism of xenobiotics, including 70% of drug molecules. CYPs are also involved in the synthesis of endogenous substrates such as steroids, fatty acids and vitamins (A and D), and less frequently mediate reduction reactions.[174,175]

Recently, certain CYPs (such as CYP1A1, 1B1, 2J1, 2S1 and 2W1) have been found to be expressed in cancer tissues mainly in solid tumours (colon, breast, lung, ovarian, oesophagus), soft tissue sarcomas and metastatic disease.[176] CYP1B1 and 1A1 are most widely present in cancer cells and are the most studied CYPs; although their mRNA is also expressed in normal cells the protein appears not to be detected at significant levels. Recently CYP2W1 has been suggested to be an interesting anticancer target. CYP2W1 is the most specific form of CYPs hitherto found; it is expressed in colon tumours.[175,177,178]

As CYPs are capable of metabolizing drugs, they potentially mediate a mechanism of drug resistance by hydroxylating lipophilic drugs leading to excretion from the cell. On the other hand, the expression of certain CYPs selectively in tumour tissues opens a window for a new and selective anticancer strategy, for example they can activate a prodrug *in situ* and thereby enhance cytotoxicity in tumour tissues.[176,174] One example is AQ4N, a bioreductive cancer drug, which is metabolized by several CYPs under hypoxic conditions, to the amine, A4Q, which is 1000-fold more toxic than AQ4N.[179]

Several other CYP-activated agents (such as resveratrol and phortress) and a CYP1B1 vaccine (Zyc300) are undergoing preclinical and clinical trials evaluations.[174,176, 178]

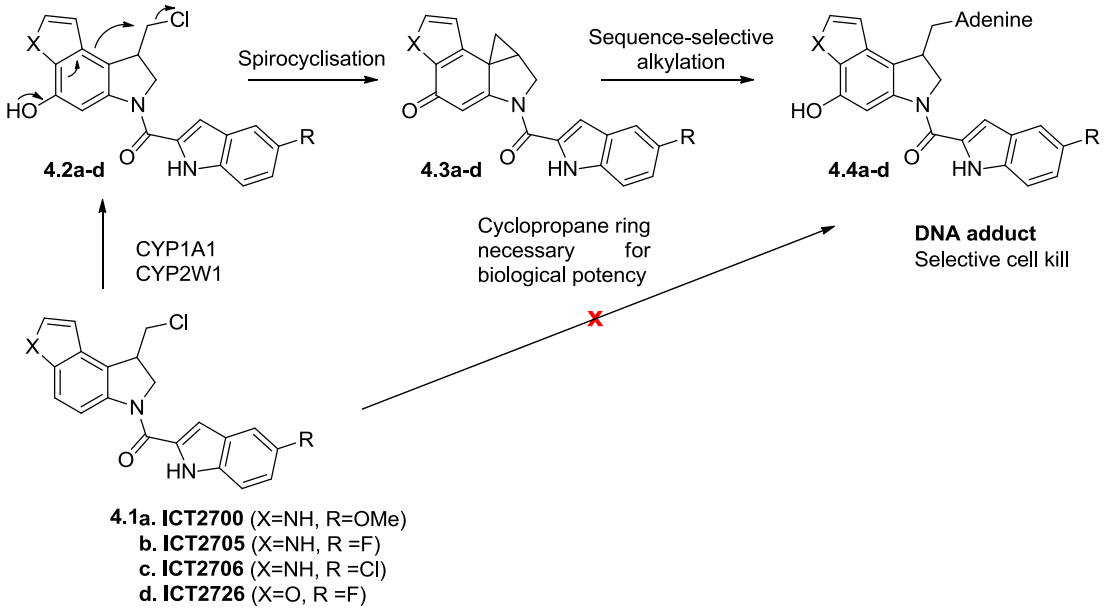
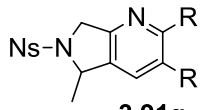
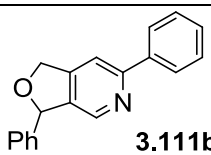
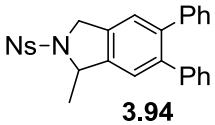
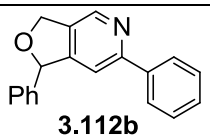
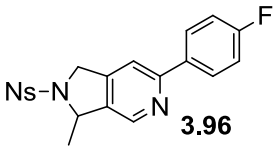
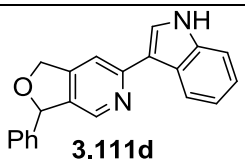
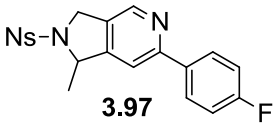
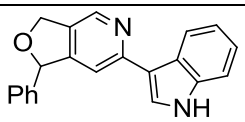
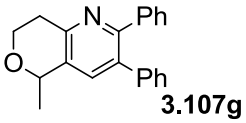
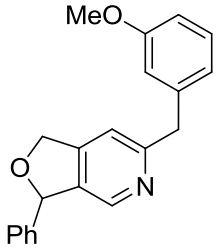
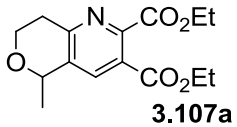
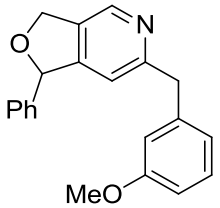
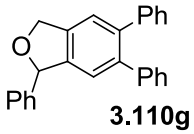
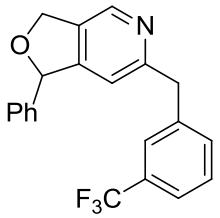


Figure 24 – Activation of duocarmycin bioprecursors derivatives 4.1a-d leading to DNA alkylation.

Work at the ICT has identified the *seco*-duocarmycin as a pharmacophore which can be re-engineered to be selectively activated by CYP1A1 or 2W1. Duocarmycins are cytotoxic natural products whose mechanism of action involves the spirocyclisation of a chloromethylindoline embedded in the duocarmycin bioprecursor scaffold to produce a cyclopropane product that is necessary for DNA alkylation and apoptosis; the cyclopropane ring is attacked by an adenine residue in the minor groove of the DNA, forming an irreversible adduct leading to cell death (Figure 24). The de-hydroxylated duocarmycins exemplified by the chloromethylindoline ICT2700 lacks biological activity before no spirocyclisation can take place unless bioactivated by a CYP. For example, cells expressing CYP1A1 are very sensitive to treatment with ICT2700 whereas 1A1-deficient cells are unaffected by treatment with this bioprecursor in vitro and in vivo.[180,181] Closely related analogues, ICT2706 and 2705, are metabolised by CYP2W1 leading to rapid tumour cell death in expressing lines CYP2W1.[29]

4.2 Biological data

Compound:number	Ref. In graphs	Compound:number	Ref. In graphs
 **3.91g**	RS-068	 **3.111b**	RS-177 F1
 **3.94**	RS-190	 **3.112b**	RS-177 F3
 **3.96**	RS-202 F1	 **3.111d**	RS-179 F1
 **3.97**	RS-202 F3	 **3.112d**	RS-179 F2
 **3.107g**	RS-115	 **3.111e**	RS-182 F1
 **3.107a**	RS-146F12	 **3.112e**	RS-182 F2
 **3.110g**	RS-149	 **3.112f**	RS-183 F2

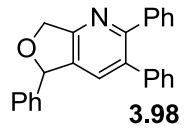
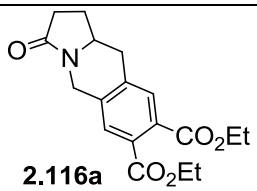
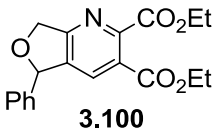
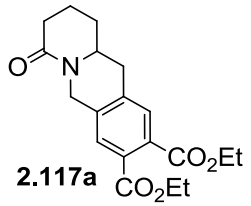
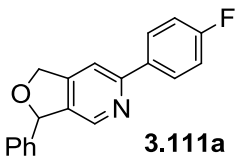
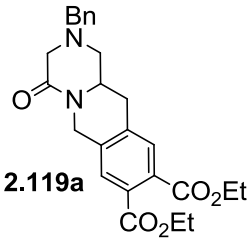
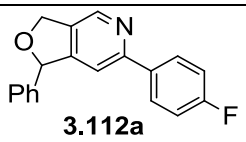
 **3.98**	RS-073	 **2.116a**	RS-5MR
 **3.100**	RS-079	 **2.117a**	RS-6MR
 **3.111a**	RS-160 F1	 **2.119a**	RS-6NBn
 **3.112a**	RS-160 F2		

Table XXXV – Compounds subjected to biological evaluation.

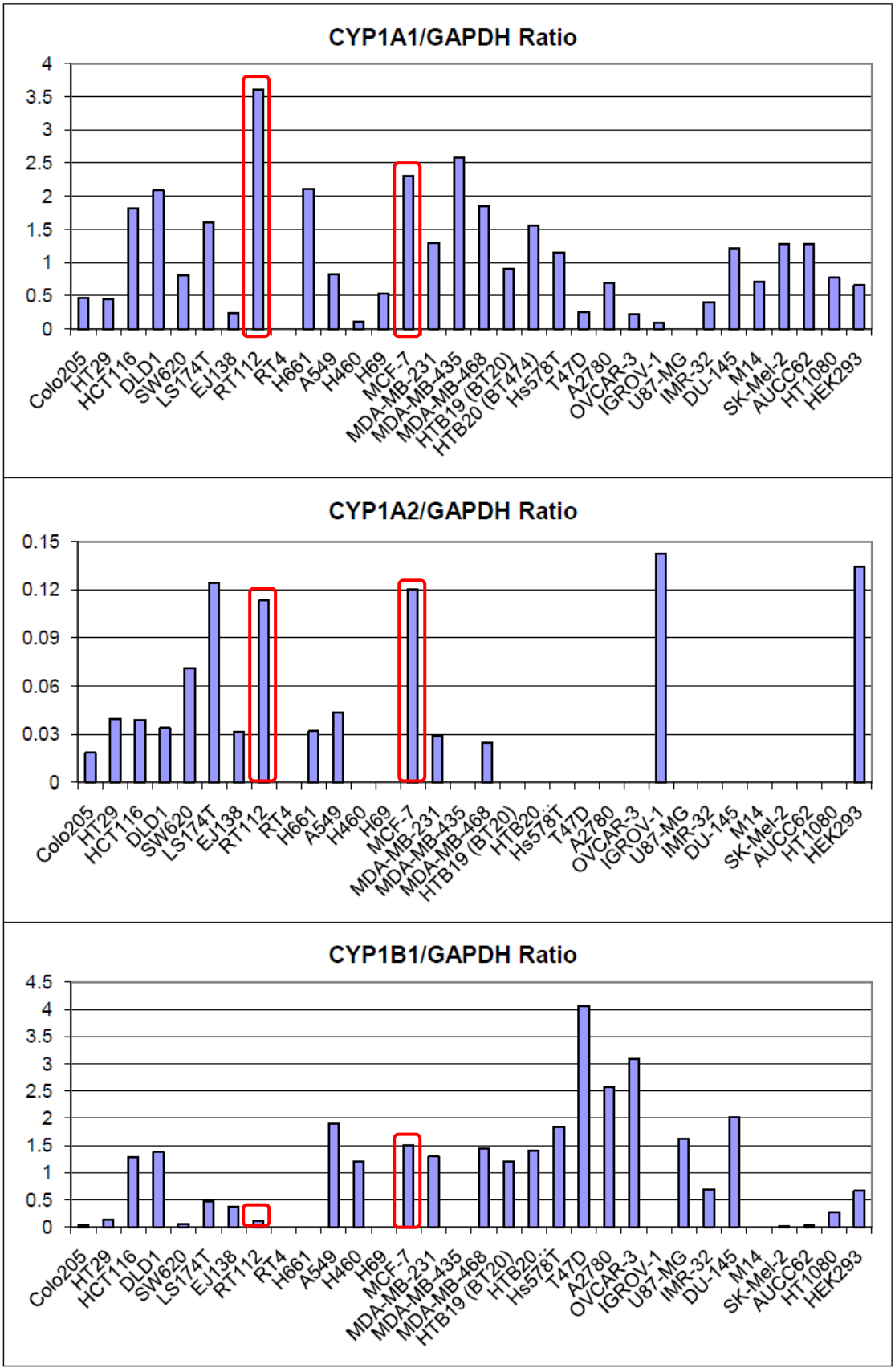


Figure 25 – Relative gene expression of CYP1A1, 1A2 and 1B1 in a panel of human cancer cell lines.

A library of 21 compounds (Table XXXV) was investigated for their cytotoxic potential in RT112 (bladder) and MCF-7 (breast) cancer cell lines. These two cancer cell lines were chosen because RT112 has moderate-to-high levels of CYP1A1 but not 1A2 or 1B1 and MCF-7 expresses both 1A1 and 1B1 (Gene expressionFigure 25, data provided by Dr Mark Sutherland (ICT, 2013)).

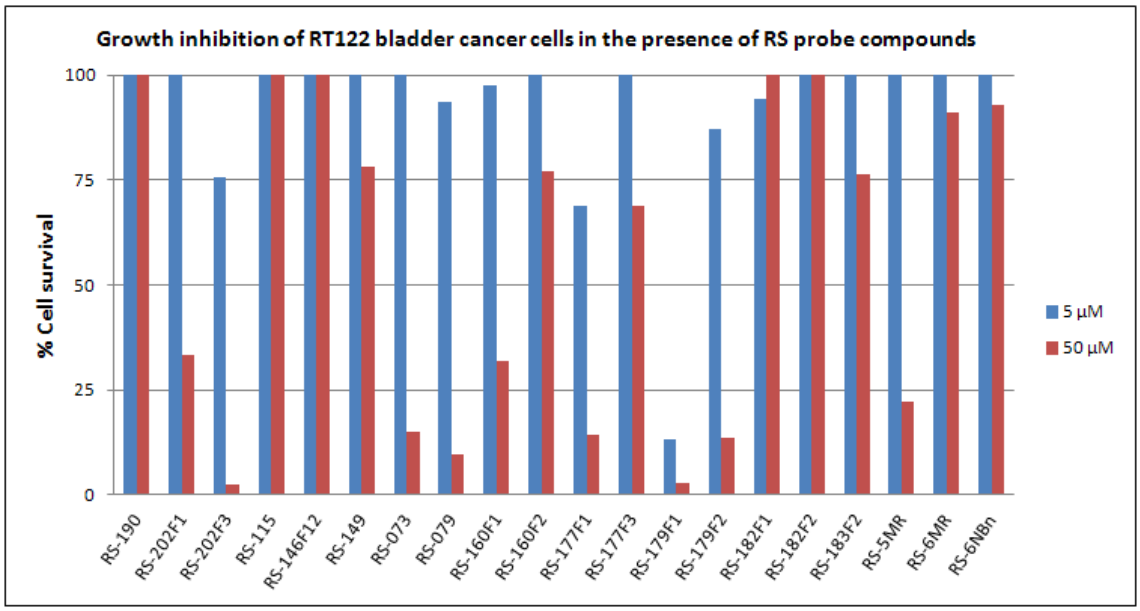


Figure 26 – Selective chemosensitivity of compounds shown in Table XXXV against RT112 bladder cancer cells.

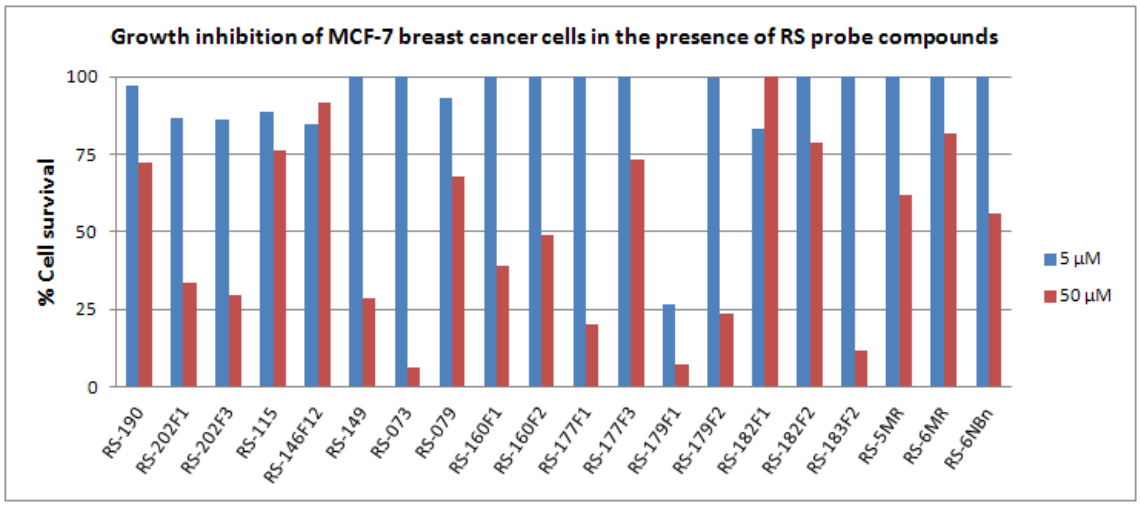
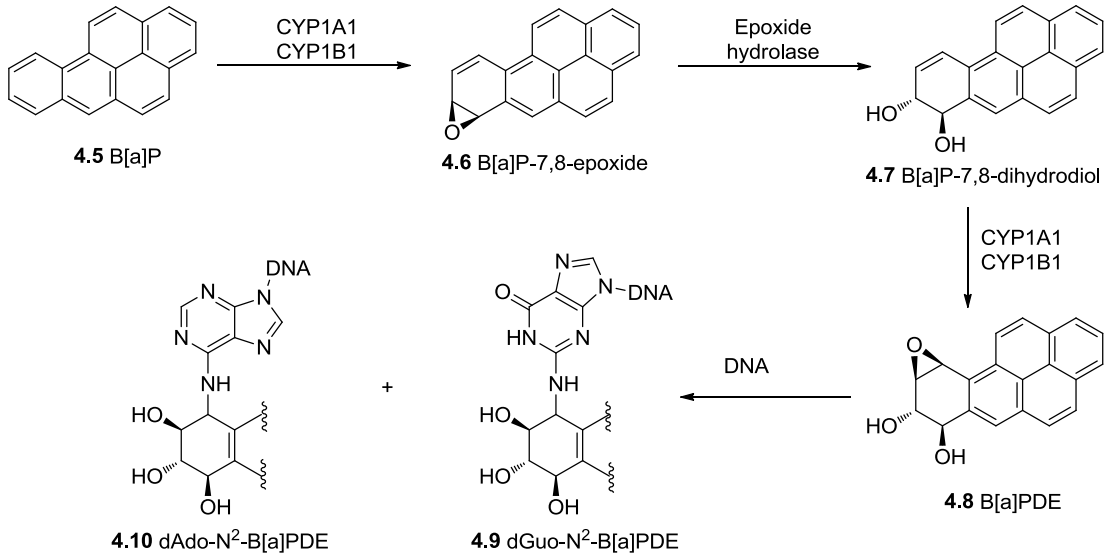


Figure 27 – Selective chemosensitivity of compounds shown in Table XXXV against MCF-7 breast cancer cells.

20 compounds were screened against RT112 bladder cancer cells and MCF-7 breast cancer cells (Figure 26 and Figure 27) at two doses 5 and 50 µM.

Compound **3.91g** (RS-068) was excluded due to problems of poor solubility. When screened at a dose of 50 μM compounds **3.100** (RS-079) and **2.116a** (RS-5MR) showed good inhibition of cell growth in the RT122 cell line and similarly compounds **3.110g** (RS-149), **3.112a** (RS-160F2), **3.112g** (RS-183F2) showed inhibition in MCF-7 cell line. However, compounds **3.96** (RS-202F1), **3.97** (RS-202F3), **3.98** (RS-073), **3.100** (RS-079), **3.111a** (RS-160F1), **3.111b** (RS-177F1), **3.111d** (RS-179F1), **3.112d** (RS-179F2) showed growth inhibition in both cell lines. When screening the compounds at a concentration of 5 μM only compound **3.111d** (RS-179F1) retained the capacity to inhibit cancer cell growth. Comparing the structure of compounds that inhibit cell growth it is hard to define a structure-activity relationship (SAR) pattern, which provides information that demonstrate why only **3.111d** (RS-179F1) is active at the lowest dose.

All the compounds were also investigated in HEK293-mock and HEK293/CYP2W1 transfected cell lines, however none of the compounds were shown to be cytotoxic at 50 μM. These results suggest that CYP2W1 is not able to activate compounds.



4.5 B[a]P
4.6 B[a]P-7,8-epoxide
4.7 B[a]P-7,8-dihydrodiol
4.8 B[a]PDE
4.9 dGuo-N^2-B[a]PDE
4.10 dAdo-N^2-B[a]PDE

Scheme 115

Compound **3.111d** (RS-179F1) is promising and more studies are needed to fully understand its mechanism of action. Nonetheless, given it is active in both RT112 and MCF-7 cells with an IC_{50} in the nano-molar range, it is possible that CYP1A1 is involved in bioactivating **3.111d** (RS-179F1) in a similar way to the

oxidation of benzo[a]pyrene (B[a]P) **4.5** by CYP1A1 and 1B1 (Scheme 115).[182] These two CYP isoforms oxidise B[a]P **4.5** to form B[a]P-7-8-epoxide **4.6** which undergoes ring-opening by epoxide hydrolase to B[a]P-7,8-dihydrodiol **4.7**. Further activation by CYP1A1 and 1B1 form a second epoxide (7,8-dihydroxy-9,10-epoxy-7,8,9-10-tetrahydrobenzo[a]pyrene (B[a]PDE) **4.8**), which is capable of crossing the nucleus membrane and react with DNA to form covalent adducts particularly at the exocyclic amines of 2'-deoxyguanosine (dGuo) **4.9** and 2'-deoxyadenosine (dAdo) **4.10** (Scheme 115). The involvement of CYP1A1 in the bioactivation of **3.111d** (RS-179F1) could be assessed by a number of experiments including incubating **3.111d** (RS-179F1) (i) with alpha-napthoflavone, a CYP1A1 inhibitor, in the chemosensitivity experiments and see if the cytotoxicity is diminished or abolished, and (ii) with CYP1A1 recombinant protein and assess metabolites to see if epoxide products are generated.

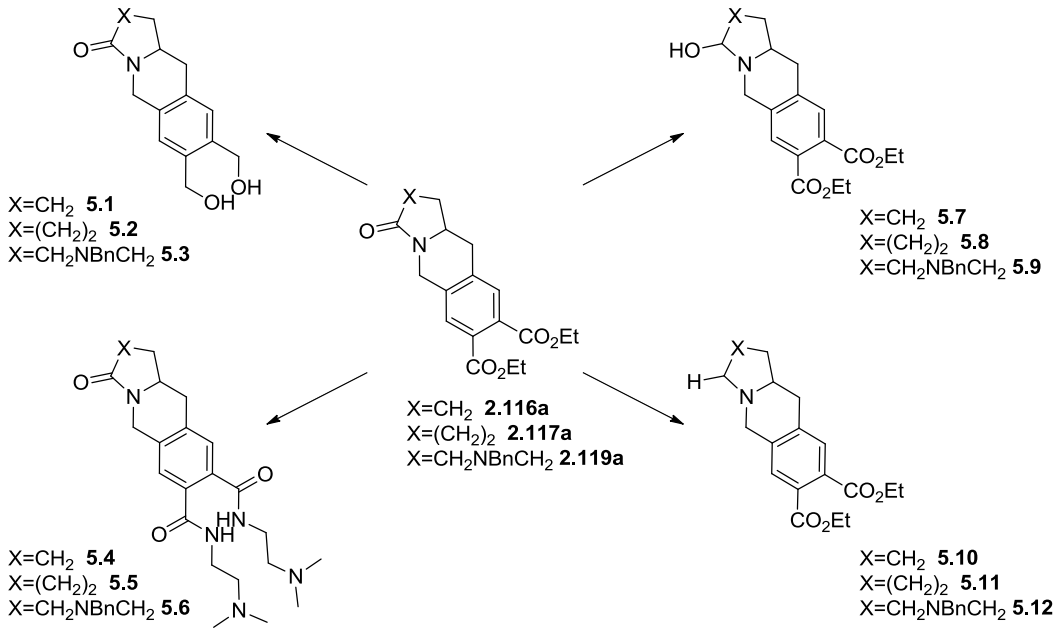
4.3 Conclusions

From the screening of the 20 compounds it can be concluded that some compounds may be bioactivated by CYP1A1 and 1B1 with **3.111d** (RS-179F1) identified as the most interesting analogue. Only one of the three compounds synthesised in Chapter 2 **2.116a** (RS-5MR) seem to have some activity when screened at 50 μM against RT112 bladder cancer cell line, which is unsurprising given these lack the key aminol fragment in the quinocarcin scaffold.

Chapter 5 Future Directions

The work generated in this thesis could be continued in several directions and some of the more immediate ones are outlined below as suggestions to future work packages:

Chapter 2 Exploration of transition-metal catalysed [2+2+2] cyclotrimerisation of alkynes in the design and synthesis of tricyclic tetrahydroisoquinoline-based molecules

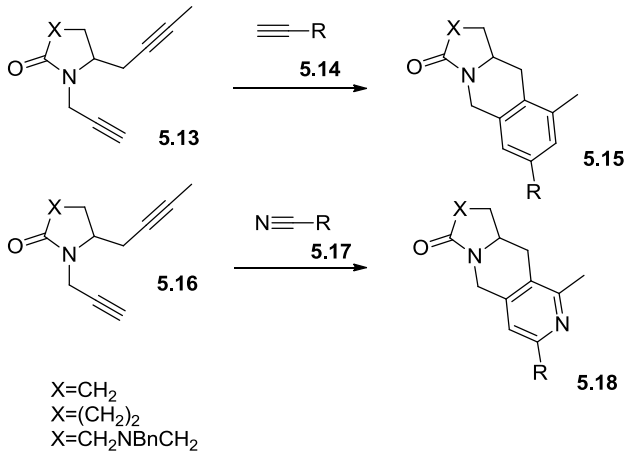


Scheme 116

(i) Derivatisation of the final tricyclic adduct to generate more enzymatically stable compounds, for example reduced derivatives such as **5.1-5-3** or amide-linked compounds with improved aqueous solubility such as **5.4-5.6** (Scheme 116).

(ii) Reduction of the carbonyl groups from the lactams **2.116a, 2.117a and 2.119a** to the correspondent amino alcohols **5.7-5.9** and amines **5.10-5.12** (Scheme 116). This will generate target compounds with an intact aminol with a simple chemical structure compared with ET-743 **1.13**. The de-hydroxy target

compounds **5.10-5.12** are likely to be inactive with a chemical structure that may be suitable for tumour-selective activation by extra-hepatic CYPs via regeneration of the aminol fragment in the resulting pharmacophore.

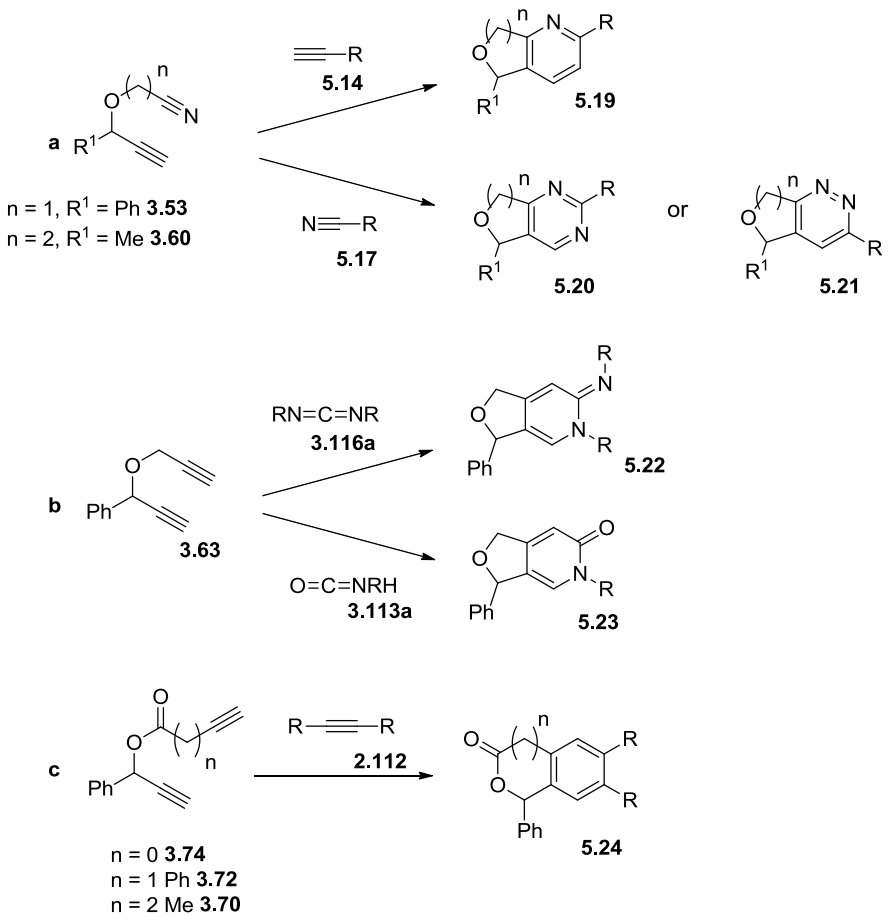


Scheme 117

(iii) Transition-metal catalysed [2+2+2] cyclotrimerisations will be performed with non-symmetric alkynes and nitriles therefore increasing the diversity of the tricyclic core library (Scheme 117)

Chapter 3 Diversity-oriented synthesis for small library synthesis *via* transition-metal catalysed [2+2+2] cyclotrimerisations under microwave irradiation

(i) Further investigation of the transition-metal mediated [2+2+2] cyclotrimerisation of the nitrogen containing compounds **3.86** and **3.89**; i.e., attempt the pairing with more symmetric and non-symmetric monoalkynes, with nitriles and other unsaturated molecules.



Scheme 118

(ii) Reaction of alkynenitriles **3.53** and **3.60** with nitriles and non-metric alkynes (Scheme 118 a)

(iii) Further interrogation of the reaction of dialkyne **3.63** with carbodiimides and isocyanates to afford iminopyridine **5.22** and pyridone **5.23** derivatives (Scheme 118 b), and the cyclisation of ester dialkynes **3.70**, **3.72** and **3.74** (Scheme 118 c).

With these approaches the diversity of the small library will be enriched and more compounds can be tested for biological activity. Compounds that show promising results in appropriate assays will be resynthesized and separation of enantiomers will be performed using a chiral stationary phase chromatography.

Chapter 4 Biological evaluation of bi- and tricyclic compounds

As mentioned in the introduction (section 1.3.1), the compounds synthesised in this thesis may have properties that are necessary for targeting the HIF-1 pathway. In the first instance, the 20 compound library will be assessed for their

ability to inhibit HIF-1 expression; this will be carried out using conventional assays that measure the gene and protein expression of this transcription factor.[23] If any of the compounds are able to inhibit HIF-1 expression, then more detailed studies will be carried out to understand where in the pathway the compounds are active.

Additionally, the compounds may possess a capacity to inhibit cell migration as discussed in the introduction (section 1.3.1). As such, the 20 compound library will be further examined in functional assays of tumour cell migration by using standard radial migration and linear scratch assays.[25]

Analogs of **3.111d** (RS-179F1) are going to be synthesised with introduction of groups stable to metabolism, for example R groups will be introduced at different positions of the indole and the phenyl group at the initial alkyne will be changed.

Chapter 6 Experimental

6.1 General methods

Commercially available reagents were used as received without additional purification. All solvents used in reactions were purchased from Sigma-Aldrich. Petroleum ether refers to the fraction of petroleum spirit boiling in the range of 60 to 80 °C. Where stated, mixtures of solvents are referred to as percentage volume to volume (v/v) ratios.

Products described in Chapter 2 were purified by flash column chromatography using Merck 9385 silica gel 60 (40-63 μm). Products described in Chapter 3 were purified using a CombiFlash companion system (Teledyne ISCO, Inc.) with pre-packed FLASH silica gel columns (Teledyne ISCO, Inc.). Analytical thin layer chromatography (TLC) was conducted on Merck silica gel 60 F_{254} aluminium backed plates. Visualisation of the reaction components was accomplished by illumination under short wavelength (254 nm) ultraviolet light or using basic potassium permanganate, phosphomolybdic acid (PMA) or vanillin stain.

All melting point (mp) values were determined on a Gallenkamp melting point apparatus and are stated uncorrected. Optical specific rotations were measured in Perkin Elmer 341 Polarimeter and are expressed in $^{o}10^{-1}cm^{2}g^{-1}$ and the concentration (c) in g/0.1 dm^{3}.

Proton Nuclear Magnetic Resonance (^{1}H NMR) spectra were recorded using Bruker AMX400 (400 MHz), JEOL ECA-600 (600 MHz), Varian I-500 (500 Mz) or Varian I-400 (400 Mz) instruments. Carbon Nuclear Magnetic Resonance (^{13}C NMR) sectra were performed in the same instruments operating at 101, 150 MHz and 126 MHz. Chemical shifts for ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from tetramethylsilane. Multiplets are reported as follow: br broad, s singlet, doublet, t triplet, q quartet, qn quintet, dd double doublet, m multiplet.

IR spectra were recorded in a PerkinElmer Spectrum 100 FT-IR Spectrometer.

Routine mass spectra were run on a Micromass Quattro Ultima spectrometer. The ionisation method (ESI or API), and mode [positive (+) or negative (-)] used are indicated for each compound. High resolution mass spectrometry was

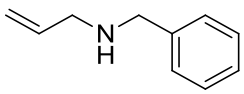
performed at the National Mass Spectrometry Centre Swansea using MAT95 or MAT900 in the electrospray ionisation (ESI) mode.

Microwave experiments were carried out in a CEM Discover microwave reactor.

Cell lines: MCF-7 human breast carcinoma cell line (was purchased from ECACC, Salisbury, UK) and RT112 human bladder carcinoma cell line were cultured in RPMI 1640 cell culture medium supplemented with 1 mM sodium pyruvate, 2 mM L-glutamine and 10% fetal bovine serum (all compounds purchased from Sigma).

6.2 Experimental procedures for Chapter 2

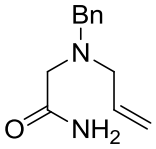
N-Benzylprop-2-en-1-amine 2.5



Using the procedure of Mukherjee and co-workers:[75] Benzyl bromide **2.3** (5.0 mL, 7.2 g, 42.0 mmol) was added *via* dropping funnel to a stirred suspension of *N*-allylamine **2.4** (25.3 mL, 19.2 g, 337 mmol) and K_2CO_3 (7.0 g, 50.4 mmol) at room temperature, under nitrogen atmosphere. After 24 h, the reaction mixture was filtered through a Celite^{TM} pad washing with DCM. After concentration under vacuum, the filtrate was purified by flash column chromatography (petroleum ether/ethyl acetate 10:1 to 2:1) affording *N,N*-allylbenzylamine **2.5** (5.1 g, 82%) as a clear oil.

R_f 0.40 (ethyl acetate/petroleum ether 1:1); δ_H (400 MHz, $CDCl_3$): 1.98 (brs, 1H, NH), 3.29 (dt, 2H, *J* 1.2 and 6.0 Hz, H1), 3.81 (s, 2H, CH_2Ph), 5.13 (dq, 1H, *J* 1.4 and 10.3 Hz, H3), 5.21 (dq, 1H, *J* 1.4 and 17.1 Hz, H3'), 5.94 (ddd, 1H, *J* 6.0, 10.3 and 17.1 Hz, H2), 7.24-7.29 (m, 1H, HAr), 7.34 (m, 4H, HAr); δ_C (100 MHz, $CDCl_3$): 51.6 (CH_2), 53.1 (CH_2), 116.2 (CH_2, C3), 127.0 (CHAr), 128.2 (CHAr), 128.4 (CHAr), 136.5 (CH, C2), 138.9 (CAr). NMR consistent with literature data.[75]

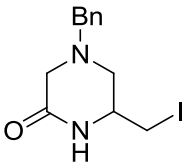
***2-(Allyl(benzyl)amino)acetamide* 2.2**



To a stirred suspension of K_2CO_3 (374 mg, 0.27 mmol) and *N,N*-allylbenzylamine **2.5** (208 mg, 136 mmol) in anhydrous acetonitrile (3.6 mL) was added 2-bromoacetamide **2.6** (216 mg, 156 mmol) at room temperature under nitrogen atmosphere. The mixture was stirred for 24 h and after that time sat. aq. $NaHCO_3$ solution (6 mL) was added. The mixture was extracted with DCM (3 × 30 mL) and the combined organic phases were dried over $MgSO_4$. After concentration under vacuum, the mixture was purified by flash column chromatography (MeOH/DCM 2:98), yielding product **2.2** (281 mg, 98%) as a white solid.

R_f 0.48 (MeOH/DCM 1:19); mp = 77-79 ºC; δ_H (400 MHz, $CDCl_3$): 3.09 (s, 2H, CH_2CONH_2), 3.13 (d, 2H, *J* 6.4 Hz, H1), 3.64 (s, 2H, CH_2Ph), 5.20-5.26 (m, 2H, H3/H3'), 5.81-5.92 (m, 1H, H2), 6.99 (br s, 1H, NH), 7.08 (brs, 1H, NH), 7.24-7.35 (m, 5H, HAr); δ_C (100 MHz, $CDCl_3$): 56.8 (CH_2), 57.3 (CH_2), 58.7 (CH_2), 118.6 (CH_2), 127.2 (CHAr), 128.3 (CHAr), 128.7 (CHAr), 134.2 (CH), 137.7 (CAr), 174.7 (C=O); ν_{max}/cm^{-1} (neat) 3384, 3187, 1651 (C=O), 1603; m/z (ESI+) 205 ($[M+H]^+$, 100%); HRMS calc. for $C_{12}H_{17}N_2O$ 205.1337, found 205.1335 $[M+H]^+$.

***4-Benzyl-6-(iodomethyl)piperazin-2-one* 2.1**

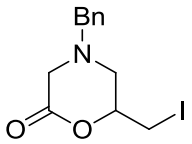


A Schlenk tube was charged with 2-(allyl(benzyl)amino)acetamide **2.2** (104 mg, 0.51 mmol), anhydrous triethylamine (150 µL, 109 mg, 1.08 mmol) and anhydrous pentane (2.0 mL) under argon. The stirred mixture was cooled to 0 °C and trimethylsilyl trifluoromethanesulfonate (195 µL, 240 mg, 1.08 mmol) was added dropwise. After stirring for 3 h at room temperature, the layers were

allowed to separate and the upper layer was transferred by cannula to another Schlenk tube. The lower layer was washed twice with Et_2O and the washings transferred to the second Schlenk tube. The combined layers were concentrated in vacuum, then cooled to 0 °C. A solution of iodine (284 mg, 1.12 mmol) in anhydrous THF (1 mL) was added. The mixture was stirred for 2 h under argon and was then quenched with an aqueous saturated solution of $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (5 mL). The reaction mixture was extracted with ethyl acetate (3 × 10mL), and the combined organic layers were dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (petroleum ether/ethyl acetate 4:1 to 1:4) affording 4-benzyl-6-(iodomethyl)piperazin-2-one **2.1** (50 mg, 30%) as a pale yellow solid and 4-benzyl-6-(iodomethyl)morpholin-2-one **2.10** (9 mg, 5%) as a yellow oil. 2-(allyl(benzyl)amino)acetamide **2.2** (18 mg, 17%) was also recovered.

R_f 0.5 (ethyl acetate); mp = 120 ºC (dec); δ_H (400 MHz, $CDCl_3$): 2.61 (dd, 1H, *J* 5.1 and 12.0 Hz, CHH'I), 2.67 (dd, 1H, *J* 4.1 and 12.0 Hz, CHH'I), 3.01 (d, 1H, *J* 16.5 Hz, H3), 3.11 (d, 1H, *J* 16.5 Hz, H3'), 3.12 (dd, 1H, *J* 6.3 and 10.0 Hz, H5), 3.26 (dd, 1H, *J* 6.8 and 10.0 H5'), 3.47 (d, 1H, *J* 13.0 Hz, CHHPh), 3.54 (d, 1H, *J* 13.0 Hz, CHH'Ph), 3.51-3.54 (m, 1H, H6), 7.20-7.29 (m, 5H, HAr); δ_C (100 MHz, $CDCl_3$): 8.5 (CH_2I), 52.8 (CH, C6), 53.0 (CH_2), 56.9 (CH_2), 61.4 (CH_2), 127.7 (CHAr), 128.6 (CHAr) 129.0 (CHAr), 136.7 (CAr), 169.8 (C=O); ν_{max}/cm^{-1} (neat) 2923, 1738 (C=O), 1627, 1380, 1244, 1197; m/z (ESI+) 331 ($[M+H]^+$, 100%); HRMS calc. for $C_{12}H_{15}N_2OI$ 331.0302, found 331.0308 $[M+H]^+$.

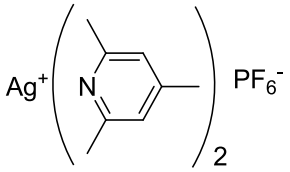
***4-Benzyl-6-(iodomethyl)morpholin-2-one* 2.10**



R_f 0.6 (ethyl acetate /petroleum ether 3:7); δ_H (400 MHz, $CDCl_3$): 2.60 (dd, 1H, *J* 7.0 and 12.5 Hz, CHHI), 2.91 (dd, 1H, *J* 3.2 and 12.5 Hz, CHH'I) 3.15 (d, 1H, *J* 17.5 Hz, H3), 3.33 (d, 1H, *J* 17.5 Hz, H3'), 3.27 (dd, 1H, *J* 4.6 and 10.3 Hz, H5), 3.33 (dd, 1H, *J* 7.9 and 10.3 H5'), 3.50 (d, 1H, *J* 12.8 Hz, CHHPh), 3.55 (d, 1H, *J* 12.8 Hz, CHH'Ph), 4.46 (m, 1H, H6), 7.19-7.31 (m, 5H, HAr); δ_C (100 MHz,

$CDCl_3$): 3.6 (CH_2I), 52.5 (CH_2), 55.0 (CH_2), 61.3 (CH_2), 77.8 (CH, C6), 129.0 (CHAr), 128.7 (CHAr) 127.9 (CHAr), 134.2 (CAr), 166.8 (C=O); ν_{max}/cm^{-1} (neat) 3190, 2850, 1698, 1650 (C=O), 1416, 1314; m/z (ESI+) 331 ($[M+H]^+$, 100%); HRMS calc. for $C_{12}H_{15}NO2I$ 332.0142, found 332.0142 $[M+H]^+$.

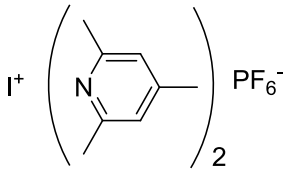
Bis(2,4,6-trimethylpyridine)silver(I) hexafluorophosphate 2.15



Using the procedure of Homsi and co-workers:[85] 2,4,6-trimethylpyridine **2.14** was added dropwise to a stirred solution of silver nitrate (5.0 g, 29.6 mmol) and potassium hexafluorophosphate (5.5 g, 29.70 mmol) in H_2O (50 mL) at 0 ºC. The reaction was allowed to warm to room temperature over 1 h, then it was filtered, and the solid washed with water, and dried *in vacuo* to yield silver *bis*(collidine) hexafluorophosphate **2.15** (14.4 g, 98%) as a white solid.

mp = 213 ºC [lit.[85] 210 ºC]; δ_H (400 MHz, $CDCl_3$): 2.42 (s, 6H, CH_3), 2.74 (s, 12H, CH_3), 7.12 (s, 4H, HAr). Data in agreement with literature.[85]

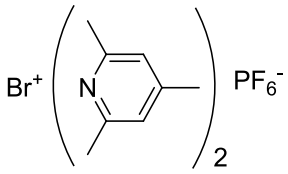
Bis(2,4,6-trimethylpyridine)iodine(I) hexafluorophosphate 2.16



Using the procedure of Homsi and co-workers:[85] a solution of iodine (1.0 g, 4.00 mmol) in anhydrous DCM (24 mL) was added dropwise to a stirred solution of silver *bis*(2,4,6-trimethylpyridine) hexafluorophosphate **2.15** (2.1 g 4.21 mmol) in anhydrous DCM (6 mL) at 0 ºC under nitrogen. The mixture was stirred at rt for 1 h and after that, a further 0.2 eq (0.4 g) of silver *bis*(2,4,6-trimethylpyridine) hexafluorophosphate **2.15** was added and the reaction mixture stirred for a further 1 h, until the iodine's colour disappeared. The reaction mixture was then filtered, washed with DCM and the filtrate concentrated *in vacuo* (maximum

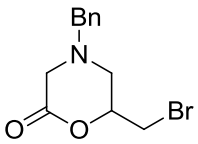
bath temperature of 22 ºC) and *bis*(2,4,6-trimethylpyridine) iodine(I) hexafluorophosphate **2.16** (1.8 g, 85%) was obtained as a pale yellow solid.
mp = 135 ºC [lit.[85] 132-133 ºC]; δ_H (400 MHz, $CDCl_3$): 2.40 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.66 (s, 6H, CH_3), 2.85 (s, 6H, CH_3), 7.13 (s, 2H, HAr), 7.16 (s, 2H, HAr). Data in agreement with literature.[85]

Bis(2,4,6-trimethylpyridine)bromine(I) hexafluorophophate 2.17



Using the procedure of Homsi and co-workers:[85] bromine (200 μL, 620 mg, 3.94 mmol) in anhydrous DCM (24 mL) was added dropwise to a stirred solution of silver *bis*(2,4,6-trimethylpyridine) hexafluorophosphate **2.15** (2.0 g, 4.06 mmol) in anhydrous DCM (6 mL) at 0 ºC under nitrogen. The mixture was stirred at rt for 1 h and after that, a further 0.2 eq (0.4 g) of the of silver *bis*(2,4,6-trimethylpyridine) hexafluorophosphate **2.15** was added and the reaction mixture stirred for a further 1 h, until the bromine's colour disappeared. The reaction mixture was filtered, washing with DCM and the filtrate concentrated *in vacuo* (maximum bath temperature of 22 ºC) to yield *bis*(2,4,6-trimethylpyridine) bromine hexafluorophosphate **2.17** (1.8 g, 95%) as a pale yellow solid.
mp = 125 ºC [lit.[85] 127-128 ºC]; δ_H (400 MHz, $CDCl_3$): 2.40 (s, 6H, CH_3), 2.70 (s, 6H, CH_3), 2.85 (s, 6H, CH_3), 7.11 (s, 4H, HAr). Data in agreement with literature.[85]

4-Benzyl-6-(bromomethyl)morpholin-2-one 2.25

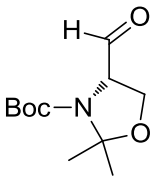


A solution of NBS (96 mg, 0.54 mmol) in dioxane (1.3 mL) was added dropwise to a stirred solution of 2-(allyl(benzyl)amino)acetamide **2.2** (100 mg, 0.49 mmol)

in a mixture of dioxane/water (680 µL, 2.25:1) at 0 ºC under nitrogen atmosphere. The mixture was stirred for 2 h at 0 ºC and then 24 h at rt. After that time, the solvents were removed under vacuum and the residue was dissolved in ethyl acetate (5 mL) and washed with brine (5 mL). The organic layer was separated, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (petroleum ether/ethyl acetate 7:3) to afford bromolactone **2.25** (28 mg, 21%) as a yellow oil and RSM **2.2** (39 mg, 39%).

R_f 0.8 (ethyl acetate); δ_H (400 MHz, $CDCl_3$): 2.63 (dd, 1H, *J* 6.9 and 12.6 Hz, C*H*H'Br), 2.85 (dd, 1H, *J* 3.4 and 12.6 Hz, CH*H*'Br), 3.16 (d, 1H, *J* 17.4 Hz, H3), 3.32 (dd, 1H, *J* 1.0 and 17.4 Hz, H3'), 3.43 (dd, 1H, *J* 4.0 and 10.5 Hz, H5), 3.47-3.52 (m, 1H, H5'), 3.50 (d, 1H, *J* 13.0 Hz, C*H*H'Ph), 3.55 (d, 1H, *J* 13.0 Hz, CH*H*'Ph), 4.60 (m, 1H, H6), 7.18-7.30 (m, 5H, HAr); δ_C (100 MHz, $CDCl_3$): 30.7 (CH_2Br), 51.2 (CH_2), 55.8 (CH_2), 61.4 (CH_2), 77.6 (CH, C6), 128.0 (CHAr), 128.7 (CHAr) 129.0 (CHAr), 135.8 (CAr), 166.8 (C=O); ν_{max}/cm^{-1} (neat) 2924, 1739 (C=O), 1632, 1245; m/z (AP+) 284 ($[M]^+$, 100% $C_{12}H_{15}{}^{79}BrN_2O$), 286 ($[M]^+$, 98% $C_{12}H_{15}{}^{81}BrN_2O$); HRMS calc. for $C_{12}H_{15}O_2N_1{}^{79}Br_1$ 284.0281, found 284.0287 $[M+H]^+$.

(*S*)-*tert*-butyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate 2.27



Via reduction with DIBAL

Using the procedure of Powell and co-workers:[98] ester **2.26** (0.9 mL, 974 mg, 3.76 mmol) was dissolved in stirring anhydrous toluene (7.8 mL) under nitrogen. After cooling to -78 ºC, DIBAL (6.6 mL of 1 M solution in THF, 6.57 mmol) was added dropwise at a rate to maintain the internal temperature below -60 ºC. The reaction was stirred for 3 h at -78 ºC and then quenched with cold methanol at a rate to maintain the internal temperature below -60 ºC. The reaction mixture was then allowed to warm to room temperature, and a 1.2 M sodium potassium tartrate solution (24 mL) was added and the mixture was stirred for 2 h until two

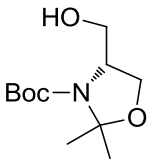
phases were observed. The reaction mixture was extracted with diethyl ether (3 × 8 mL) and the combined organic layers dried over Na_2SO_4, concentrated in vacuum and purified by flash column chromatography (ethyl acetate/petroleum ether 1:9 to 1:4) to yield aldehyde **2.27** (813 mg, 94%) as a clear oil.

R_f 0.53 (petroleum ether/ethyl acetate 7:3); $[\alpha]_D^{20}$ = -94.5 (c 1.1, $CHCl_3$), [lit.[99] $[\alpha]_D^{20}$ = -93.3 (c 1.1, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$): 1.36 (s, 5H, CH_3), 1.44 (s, 6H, CH_3), 1.49 (s, 2H, CH_3), 1.53 (s, 1H, CH_3), 1.58 (s, 1H, CH_3), 3.96-4.05 (m, 2H), 4.13-4.28 (m, 1H), 9.48 (d, 0.61 H, *J* 1.9 Hz, CHO), 9.53 (brs 0.39 H, *J* 1.9 Hz, CHO). Most peaks are doubled due to restricted rotation of NBOC group. Data in agreement with literature.[99]

Via reduction with $LiAlH_4$ followed by Swern oxidation

Using the procedure of Dondoni and co-workers:[99] Ester **2.26** (231 µL, 250 mg, 0.96 mmol) in anhydrous THF (1.3 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (55 mg, 1.44 mmol) in anhydrous THF (2.5 mL) at room temperature under argon. After 1.5 h, the reaction mixture was cooled to 0 ºC and a solution of NaOH (10%, 3 mL) was added dropwise and the resulting mixture stirred at rt for 1 h. The white precipitate was filtered through a pad of Celite™ and washed with Et_2O. The filtrate was washed with phosphate buffer (pH = 7.4), and the aqueous layer extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum, to yield alcohol **2.30** (276 mg, 100%) as yellow pale oil.

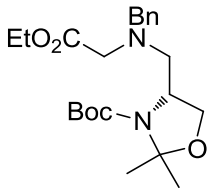
(*R*)-*Tert*-butyl 4-(hydroxymethyl)-2,2-dimethyloxazolidine-3-carboxylate 2.30



R_f 0.29 (petroleum ether/ethyl acetate 7:3); $[\alpha]_D^{20}$ = +23.0 (c 5.0, $CHCl_3$), [lit.[99] $[\alpha]_D^{20}$ = +22.1 (c 1.5, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$): 1.41(br s, 12 H, CH_3), 1.47 (s, 3H, CH_3), 3.44 (brs, 1H, OH), 3.48 (dd, 1H, *J* 5.6 and 10.7 Hz), 3.68-3.71 (m, 1H), 3.76-3.78 (m, 1H), 3.91-3.97 (m, 2H). Data in agreement with literature.[99]

Oxalyl chloride (640 µL of a 2 M solution in DCM, 1.28 mmol) was dissolved in stirred anhydrous THF (5.0 mL) under argon. The reaction was cooled to -78 °C and DMSO (181 µL, 199 mg, 2.55 mmol) was added dropwise and the reaction was stirred for 10 minutes. A solution of alcohol **2.30** (184 mg, 0.80 mmol) in THF (5.0 mL) was then added dropwise and the reaction mixture stirred for 20 minutes. DIPEA (890 µL, 660 mg, 5.11 mmol) was added dropwise and the reaction mixture was stirred for 1 h at -78 °C and a further 1 h at rt. After that time, the reaction was quenched with water (3 mL), extracted with ethyl acetate (3 × 3 mL) and the organic layer dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate/petroleum ether 1:9) to yield aldehyde **2.27** (94 mg, 52%) as a pale yellow liquid.

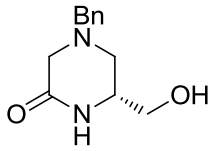
(*R*)-*Tert*-butyl 4-((benzyl(2-ethoxy-2-oxoethyl)amino)methyl)-2,2-dimethyloxazolidine-3-carboxylate 2.29



Using the procedure of Powel et al:[98] Sodium cyanoborohydride (622 mg, 9.90 mmol) was added to a stirred solution of aldehyde **2.27** (1.5 g, 6.34 mmol) and acetic acid (676 µL, 710 mg, 11.81 mmol) in methanol (20 mL) at 0 ºC under nitrogen. After 18 h the reaction was quenched with solid K_2CO_3 (large excess). The solvent was evaporated and the residue was dissolved in DCM and washed with a mixture of H_2O/sat. $NaHCO_3$/brine (5 mL 1:1:1). The aqueous layer was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers dried over Na_2SO_4, concentrated in vacuum and purified by flash column chromatography (ethyl acetate/petroleum ether 1:4) affording amine **2.29** (1.4 g, 55%) as a pale yellow oil.

R_f 0.65 (petroleum ether/ethyl acetate 7:3); $[\alpha]_D^{20}$ = -68.0 (c 2.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.22-1.27 (m, 3H), 1.43-1.47 (m, 12H), 1.54 (s, 3H), 2.58-2.64 (m, 1H), 2.98 (d, 1 H, *J* 12.5 Hz), 3.27 (d, 1H, *J* 17.6 Hz, C*H*H'Ph), 3.33 (d, 1H, *J* 17.6 Hz, CH*H*'Ph), 3.70-3.76 (m, 1H), 3.88-3.95 (m, 2H), 4.00 (d, 1H, *J* 10.0 Hz), 4.05 (d, 1H, *J* 10.0 Hz), 4.11-4.18 (m, 1H), 7.24-7.52 (m 5H, HAr). NMR in agreement with literature.[98]

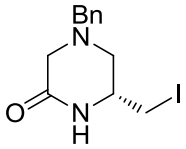
(*R*)-4-Benzyl-6-(hydroxymethyl)piperazin-2-one 2.23



Using the procedure of Powel et al:[98] an aqueous solution of 6.0 M HCl (10.0 mL) was added to a stirred solution of amine **2.29** (1.5 g, 3.57 mmol) in MeOH (18 mL) under nitrogen and the reaction mixture heated to reflux for 19 h. The reaction mixture was cooled to rt and neutralized with an aq. sat. solution of $NaHCO_3$. The methanol was removed under vacuum and the residue was dissolved in DCM (90 mL) and washed with H_2O/brine (1:1, 90 mL). The aqueous layer was extracted with DCM (3 × 90 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuum, to yield alcohol **2.23** (635 mg, 81%) as a pale pink solid.

R_f 0.37 (DCM/Methanol 9:1); mp: 77 – 83 ºC; $[\alpha]_D^{20}$ = -32.5 (c 4.0, $CHCl_3$), [lit.[98] $[\alpha]_D^{20}$ = -34.0 (c 11.4, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$): 2.37 (dd, 1H, *J* 5.7 and 11.7 Hz, H5), 2.62 (dd, 1H, *J* 3.6 and 11.7 Hz, H5'), 2.99 (d, 1H, *J* 16.7 Hz, H3), 3.04 (d, 1H, *J* 16.7 Hz, H3'), 3.39-3.55 (m, 5H, H6, CHH'OH, CHH'Ph), 4.33 (br s, 1H, OH), 7.31-7.11 (m, 5H, HAr), 7.57 (s, 1H, NH); δ_C (100 MHz, $CDCl_3$): 51.1 (CH_2, C5), 52.7 (CH, C6), 56.6 (CH_2, C3), 61.8 (CH_2Ph), 65.2 (CH_2OH), 127.7 (CHAr), 128.6 (CHAr), 129.0 (CHAr), 136.4 (CAr), 170.3 (C=O); m/z (ESI+) 220 $[M+H]^+$, 100%. Data in agreement with literature.[98]

***(R)-4-benzyl-6-(iodomethyl)piperazin-2-one* 2.1**



Via reaction with methyl triphenoxy phosphonium iodide ($P(PhOMe)_3MeI$)

$P(PhOMe)_3MeI$ (204 mg, 0.452 mmol) was added to a solution of alcohol **2.23** (50 mg, 0.23 mmol) in anhydrous THF (3.0 mL) at 0 ºC under nitrogen. After 2 h, the reaction mixture was quenched with methanol (3 mL) and the solvents were evaporated under vacuum. The residue was dissolved in DCM (4 mL) and washed with an aq. sat. solution of $Na_2S_2O_3$. The aqueous phase was then extracted with DCM (3 × 4 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (ethyl acetate/petroleum ether 1:1) yielded iodolactam **2.1** (35 mg, 47%) as a yellow solid.

mp = 120 ºC (dec); $[\alpha]_D^{20}$ = +1.8 (c 3.8, $CHCl_3$). The rest of the data is identical to the racemic compound previously obtained.

Via reaction with phosphine polymer support

A solution of iodine (75 mg, 0.30 mmol) in anhydrous toluene (2.0 mL) was added dropwise to a stirred slurry of alcohol **2.23** (50 mg, 0.23 mmol), imidazole (39 mg, 0.57 mmol) and triphenylphosphine polymer bound (166 mg of 3 mmol/g loaded polymer) in anhydrous toluene (2.0 mL) at room temperature under nitrogen. The reaction mixture was heated at 50 ºC for 5 h, cooled to rt, and filtered through a pad of Celite™ washing with DCM (5 mL). The filtrate was washed with an aq. sat. solution of $NaHCO_3$ (5 mL), dried over $MgSO_4$ and concentrated under vacuum to yield iodolactam **2.1** (61 mg, 86%).

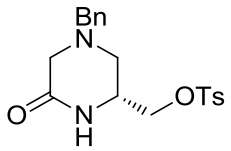
Via Finkelstein Reaction

TsCl (52 mg, 0.27 mmol) was added to a stirred solution of alcohol **2.23** (50 mg, 0.23 mmol) and NEt_3 (63 µL, 46 mg, 0.45 mmol) in anhydrous DCM (1.5 mL) at room temperature under nitrogen. DMAP (cat.) was added and the reaction mixture stirred overnight. The solvents were evaporated under vacuum and the

residue purified by flash column chromatography (petroleum ether/ethyl acetate 7:3) affording tosylate **2.31** (79 mg, 88%) as a yellow oil.

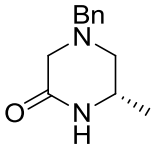
Tosylate **2.31** (97 mg, 0.21 mmol) was then dissolved in stirred acetonitrile (4.0 mL) and NaI (95 mg, 0.63 mmol) was added under N_2, and the reaction mixture was heated at reflux for 24 h. After cooling to rt the precipitate was filtered off and the solution was concentrated under vacuum. The residue was dissolved with DCM (3 mL) and washed with an aq. sat. solution of $Na_2S_2O_3$. The aqueous layer was extracted with DCM (3 $\times$ 3mL), the combined organic layers dried over $MgSO_4$ and concentrated under reduced pressure to yield iodolactam **2.1** (79 mg, 89%) as a thick yellow oil.

***(R)-(4-Benzyl-6-oxopiperazin-2-yl)methyl 4-methylbenzenesulfonate* 2.31**



R_f 0.20 (ethyl acetate); $[\alpha]_D^{20}$ = -38.1 (c 1.6, $CHCl_3$) ; δ_H (400 MHz, $CDCl_3$): 2.30 (s, 3H, CH_3), 2.46 (dd, 1H, *J* 4.0 and 12.1 Hz, H3), 2.53 (dd, 1H, *J* 3.9 and 12.1 Hz, H3'), 2.80 (d, 1H, *J* 16.7 Hz, H5), 3.03 (d, 1H, *J* 16.7 Hz, H5'), 3.35 (d, 1H, *J* 13.0 Hz, C*H*H'Ph), 3.40 (d, 1H, *J* 13.0 Hz, CH*H*'Ph), 3.54 (m, 1H, H2), 3.89 (dd, 1H, *J* 6.1 and 9.5 Hz, C*H*H'OTs), 4.03 (dd, 1H, *J* 7.1 and 9.5 Hz, CH*H*'OTs), 7.09-7.11 (m, 2H, HAr), 7.17-7.26 (m, 5H, HAr), 7.66-7.68 (m, 2H, HAr); δ_C (100 MHz, $CDCl_3$): 21.7 (CH_3), 49.7 (CH_2, C3), 50.3 (CH, C2), 56.7 (CH_2, C5), 61.5 (CH_2Ph), 70.4 (CH_2OTs), 127.8 (CAr), 128.0 (CHAr), 128.6 (CHAr), 128.9 (CHAr), 130.1 (CHAr), 132.3 (CAr), 145.4 (CAr) ; ν_{max}/cm^{-1} (neat) 3628, 2965, 1672 (C=O), 1627, 1360, 1173; m/z (ESI+) 375 ($[M+H]^+$, 100%); HRMS calc. for $C_{19}H_{23}N_2O_4S$ 375.1373, found 375.1376 $[M+H]^+$.

***(S)-4-Benzyl-6-methylpiperazin-2-one* 2.34**

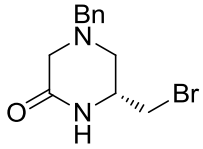


Preparation of organozinc intermediate: A Schlenk tube was charged with Zn dust (40 mg, 0.61 mmol) and purged with argon. Anhydrous THF (400 µL) and 1,2-dibromoethane (2.5 µL, 5 mg, 0.03 mmol) were added and the stirred mixture was thrice heated to reflux with a hot-air gun and allowed to cool to rt. TMSCl (19 µL, 16 mg, 0.07 mmol) was added and the mixture stirred for 6 minutes. To this activated zinc was added a solution of iodolactam **2.1** (100 mg, 0.30 mmol) in anhydrous THF (100 µL). The mixture was stirred for 4.5 h. The excess of zinc was allowed to settle and the resulting solution employed in the next step of the reaction.

Coupling reaction: CuCN (27 mg, 0.30 mmol) was added to a solution of LiCl (36 mg, 0.86 mmol, freshly dried under vacum at 50 ºC) in stirred anhydrous THF (200 µL). After the solution become yellow, it was cooled to -10 ºC and the solution of organozinc **2.32** previous formed was added dropwise *via* syringe. The solution was stirred for 12 minutes and then cooled to -78 °C. Propargyl bromide **2.9** (27 µL of an 80% solution in toluene, 0.24 mmol) was added and the reaction was stirred for 2 h at -20 ºC and then at rt overnight. The reaction was quenched with an aq. sat. solution of NH_4Cl (3 mL), extracted with ethyl acetate (3 × 3 mL), dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (95:5 DCM/MeOH) to yield amine **2.2** (10 mg, 17%) as white solid followed by lactam **2.34** (38 mg, 61%) as a white solid.

R_f 0.46 (DCM/Methanol 9:1); mp = 120 ºC (dec); $[\alpha]_D^{20}$ = -10.9 (c 19.0, $CHCl_3$) ; δ_H (400 MHz, $CDCl_3$): 1.08 (d, 3H, *J* 6.4 Hz, CH_3), 2.04 (dd, 1H, *J* 8.4 and 11.6 Hz, H5), 2.74 (dd, 1H, *J* 4.0 and 11.6 Hz, H5'), 2.88 (d, 1H, *J* 16.5 Hz, H3), 3.21 (dd, 1H, *J* 1.1 and 16.5 Hz, H3'), 3.46 (d, 1H, *J* 13.1 Hz, C*H*H'Ph), 3.51 (d, 1H, *J* 13.1 Hz, CH*H*'Ph), 3.54-3.61 (m, 1H, H6), 6.53 (brs, 1H, NH), 7.18-7.28 (m, 5H, HAr); δ_C (100 MHz, $CDCl_3$): 20.1 (CH_3), 47.6 (CH, C6), 55.8 (CH_2), 56.6 (CH_2), 61.7 (CH_2), 127.5 (CHAr), 128.4 (CHAr) 129.0 (CHAr), 137.0 (CAr), 169.7 (C=O); ν_{max}/cm^{-1} (neat) 3226, 2821, 1669 (C=O), 1454; m/z (ESI+) 205 ($[M+H]^+$, 100%); HRMS calc. for $C_{12}H_{17}N_2O$ 205.1335, found 205.1334 $[M+H]^+$.[183]

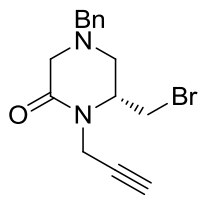
***(R)-4-Benzyl-6-(bromomethyl)piperazin-2-one* 2.38**



NaH (6 mg of a 60% suspension in mineral oil, 0.02 mmol) was added to a stirred solution of tosylate **2.31** (50 mg, 0.13 mmol) in anhydrous DMF (0.5 mL) at rt, under nitrogen. After 30 minutes propargyl bromide **2.9** (31 µL of an 80% solution in toluene, 0.28 mmol) was added and the reaction was stirred for 19 h. The reaction mixture was quenched with an aq. sat. solution of NH_4Cl (3 mL), extracted with ethyl acetate (3 × 3 mL) and the combined organic layers dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography (3% MeOH/DCM) to yield bromolactam **2.38** (10 mg, 26%), bromoalkyne **2.39** (3 mg, 7%) and bromoallene **2.40** (3 mg, 7%) as yellow oils.

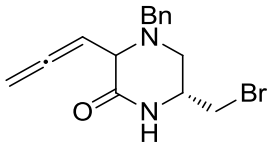
R_f 0.56 (DCM/MeOH 9:1); $[\alpha]_D^{20}$ = -5.1 (c 2.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 2.58 (dd, 1H, *J* 4.6 and 11.8 Hz, H5), 2.65 (dd, 1H, *J* 4.0 and 11.8 Hz, H5'), 3.04 (d, 1H, *J* 16.7 Hz, H3), 3.16 (d, 1H, *J* 16.7 Hz, H3'), 3.32 (dd, 1H, *J* 10.1 and 6.7 Hz, C*H*H'Br), 3.42 (dd,1H, *J* 10.1 and 6.7 Hz, CH*H*'Br), 3.48 (d, 1H, *J* 13.0 Hz, C*H*H'Ph), 3.53 (d, 1H, *J* 13.1 Hz, CH*H*'Ph), 3.58-3.64 (m, 1H, H6), 6.05 (s, 1H, NH), 7.22-7.29 (m, 5H, HAr); δ_C (100 MHz, $CDCl_3$): 34.7 (CH_2), 51.8 (CH, C6), 52.7 (CH_2), 57.0 (CH_2), 61.4 (CH_2), 127.7 (CHAr), 128.6 (CHAr), 128.9 (CHAr), 136.6 (CAr), 169.4 (C=O); ν_{max}/cm^{-1} (neat) 3299, 2920, 2776, 1668 (C=O), 1623, 1476, 1462; m/z (ESI+) 283 ($[M]^+$, 100% $C_{12}H_{15}{}^{79}BrN_2O$), 285 ($[M]^+$, 98% $C_{12}H_{15}{}^{81}BrN_2O$) $[M]^+$; HRMS calc. for $C_{12}H_{16}N_2O^{79}Br$ 283.0441, found 283.0436 $[M+H]^+$.

***(R)-4-Benzyl-6-(bromomethyl)-1-(prop-2-yn-1-yl)piperazin-2-one* 2.39**



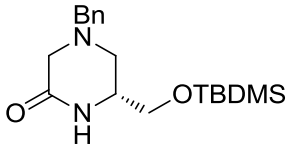
R_f 0.82 (DCM/Methanol 9:1); $[\alpha]_D^{20}$ = -3.5 (c 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 2.22 (t, 1H, *J* 2.5 Hz, C≡CH), 2.47 (dd, 1H, *J* 2.4 and 12.2 Hz, H5), 2.89 (d, 1H, *J* 16.8 Hz, H3), 3.15-3.19 (m, 1H, H5'), 3.36 (dd, 1H, *J* 1.5 and 16.8 Hz, H3'), 3.49 (d, 1H, *J* 13.0 Hz, C*H*H'Ph), 3.50 (dd, 1H, *J* 1.4 and 6.8 Hz, C*H*H'Br),3.53 (d, 1H, *J* 13.0 Hz, CH*H*'Ph), 3.67-3.76 (m, 2H, CH*H*'Br and H6), 3.88 (dd, 1H, *J* 2.5 and 17.8 Hz, NC*H*H'C≡C), 4.53 (dd, 1H, *J* 2.5 and 17.8 Hz, NCH*H*'C≡C), 7.20-7.32 (m, 5H, HAr); δ_C (100 MHz, $CDCl_3$): 30.4 (CH_2, CH_2Br), 34.01 (CH_2, NCH_2), 50.9 (CH_2, C5), 57.3 (CH, C6), 57.4 (CH_2, C3), 61.5 (CH_2, CH_2Ph), 73.2 (C, C≡C), 78.0 (CH, C≡CH), 127.8 (CHAr), 128.6 (CHAr), 129.1 (CHAr), 136.7 (CAr), 167.3 (C=O); ν_{max}/cm^{-1} (neat) 3300, 3055, 2925, 2849, 2805, 1655 (C=O), 1264; m/z (ESI+) 321 ($[M]^+$, 100% $C_{12}H_{15}{}^{79}BrN_2O$), 323 ($[M]^+$, 98% $C_{12}H_{15}N_2O^{81}Br$); HRMS calc. for $C_{15}H_{18}N_2O^{79}Br$ 321.0597, found 321.0602 $[M+H]^+$.

***(6R)-4-Benzyl-6-(bromomethyl)-3-(propa-1,2-dien-1-yl)piperazin-2-one* 2.40**



R_f 0.65 (DCM/Methanol 9:1); $[\alpha]_D^{20}$ = -34.0 (c 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 2.40 (dd,1H, *J* 5.1 and 12.3 Hz, H5), 2.97 (dd, 1H, *J* 4.0 and 12.3 Hz, H5'), 3.26 (dd, 1H, *J* 8.0 and 10.0 Hz, C*H*H'Br) , 3.34 (dd, 1H, *J* 5.4 and 10.0 Hz, CH*H*'Br) , 3.46 (d, 1H, *J* 13.3 Hz, C*H*H'Ph), 3.50-3.57 (m, 1H, H6), 3.79 (d, 1H, *J* 7.0 Hz, H3) , 3.81 (d, 1H, *J* 13.3 Hz, CH*H*'Ph), 4.90- 4.80 (m, 2H, =CHH'), 5.25 (dt, 1H, *J* 7.0 and 8.1 Hz, =CH) , 6.17 (br s, 1H, NH), 7.31-7.20 (m, 5H, HAr); δ_C (100 MHz, $CDCl_3$): 35.1 (CH_2, CH_2Br), 47.7 (CH_2, C5), 52.8 (CH, C6), 57.9 (CH_2, CH_2Ph), 64.5 (CH, C3), 76.9 (CH_2, $=CH_2$), 85.3 (CH, =CH), 127.7 (CHAr), 128.6 (CHAr), 129.0 (CHAr), 137.5 (CAr), 169.8 (C=O), 210.5 (C, =C=); ν_{max}/cm^{-1} (neat) 3287, 2962, 2923, 2840, 1950, 1666 (C=O), 1619, 1455, 1061; m/z (ESI+) 321 ($[M]^+$, 100% $C_{12}H_{17}{}^{79}BrN_2O$), 323 ($[M]^+$, 98% $C_{12}H_{17}{}^{81}BrN_2O$); HRMS calc. for $C_{15}H_{18}N_2O^{79}Br$ 321.0597, found 321.0594 $[M+H]^+$.

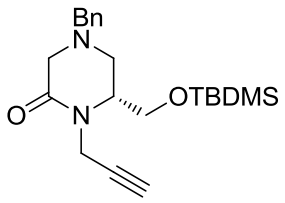
***(R)-4-Benzyl-6-(((tert-butyldimethylsilyl)oxy)methyl)piperazin-2-one* 2.45**



TBDMSCl (82 mg, 0.55 mmol) was added to a stirred solution of alcohol **2.23** (100 mg, 0.45 mmol) and imidazole (46 mg, 0.68 mmol) in anhydrous DCM (2.0 mL) at room temperature under nitrogen, and the reaction mixture was stirred overnight. The reaction mixture was diluted with DCM (5 mL) and quenched with water (5 mL). The aqueous layer was extracted with ethyl acetate (3 $\times$ 5 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to yield the protected alcohol **2.45** (130 mg, 85%) as a yellow oil.

R_f 0.54 (ethyl acetate); $[\alpha]_D^{20}$ = -35.9 (c 2.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 0.00 (s, 3H, CH_3), 0.01 (s, 3H, CH_3), 0.83 (s, 9H, $C(CH_3)_3$), 2.27 (dd, 1H, *J* 6.5 and 11.7, H5) , 2.68 (dd, 1H, *J* 3.6 and 11.7, H5'), 3.01 (brd, 1H, *J* 16.5 Hz, H3) , 3.18 (dd, 1H, *J* 0.8 and 16.5 Hz, H3') , 3.45 (dd, 1H, *J* 1.6 and 8.4 Hz, C*H*H'OTBDMS) , 3.48 (d, 1H, *J* 13.1 Hz, C*H*H'Ph) , 3.42-3.60 (m, 1H, H6), 3.55 (d, 1H, *J* 13.1 Hz, CH*H*'Ph), 3.58 (dd, 1H, *J* 2.8 and 8.4 Hz, CH*H*'OTBDMS), 6.26 (s, 1H, NH), 7.18-7.35 (m, 5H, HAr); δ_C (100 MHz, $CDCl_3$): -5.4 (CH_3), -5.4 (CH_3), 18.2 (C), 25.8 (CH_3), 50.3 (CH_2), 53.3 (CH), 57.0 (CH_2), 61.7 (CH_2), 64.9 (CH_2), 127.6 (CHAr), 128.5 (CHAr), 129.0 (CHAr), 136.9 (CAr), 169.3 (C=O); ν_{max}/cm^{-1} (neat) 3299, 2954, 2931, 2850, 1651 (C=O), 1444, 1430, 1231; m/z (ESI) 335 $[M+H]^+$, 100%. The sample decomposed before HRMS could be obtained.

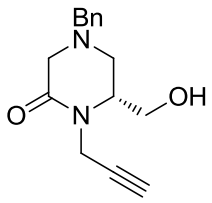
***(R)-4-Benzyl-6-(((tert-butyldimethylsilyl)oxy)methyl)-1-(prop-2-yn-1-yl)piperazin-2-one* 2.46**



NaH (18 mg of a 60% suspension in mineral oil, 0.45 mmol) was added to a stirred solution of protected alcohol **2.45** (126 mg, 0.38 mmol) in anhydrous THF (2.0 mL) at rt under nitrogen. After 30 minutes propargyl bromide **2.9** (88 µL of an 80% solution in toluene, 0.28 mmol) was added and the reaction mixture stirred for 21 h. The reaction mixture was quenched with an aq. sat. solution of NH_4Cl (3 mL), extracted with ethyl acetate (3 × 3 mL) and the combined organic layers dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate/petroleum ether 1:1) to afford alkyne **2.46** (76 mg, 54%) as a yellow oil and recovered starting material **2.45** (37 mg, 30%).

R_f 0.63 (ethyl acetate/petroleum ether 1:1); $[\alpha]_D^{20}$ = -6.0 (c 5.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): -0.02 (s, 3H, CH_3), 0.00 (s, 3H, CH_3) , 0.81 (s, 9H, $C(CH_3)_3$), 2.17 (t, 1H, *J* 2.5 Hz, C≡CH), 2.43 (dd, 1H, *J* 3.9 and 11.9 Hz, H5), 2.85 (brd, 1H, *J* 16.6 Hz, H3), 2.98 (dm, 1H, *J* 2.2 and 11.9 Hz, H5') , 3.30 (dd, 1H, *J* 1.4 and 16.6 Hz, H3'), 3.44 (d, 1H, *J* 13.0 Hz, C*H*H'Ph), 3.50 (d, 1H, *J* 13.0 Hz, CH*H*'Ph), 3.53-3.58 (m, 1H, H6), 3.75 (dd, 1H, *J* 3.8 and 8.6 Hz, C*H*H'OTBDMS), 3.78 (dd, 1H, *J* 6.5 and 8.5 Hz, CH*H*'OTBDMS), 3.85 (dd, 1H, *J* 2.5 and 17.5 Hz, NC*H*H'C≡C), 4.64 (dd, 1H, *J* 2.5 and 17.5 Hz, NCH*H*'C≡C), 7.17-7.29 (m, 5H, HAr); δ_C (100 MHz, $CDCl_3$): -5.5 (CH_3), -5.4 (CH_3), 18.2 (C*t*-Bu), 25.8 (CH_3), 34.2 (CH_2), 50.8 (CH_2), 57.2 (CH, C6), 57.2 (CH_2), 61.8 (CH_2), 62.2 (CH_2), 72.0 (C, C≡C), 78.7 (CH, C≡CH), 127.5 (CHAr), 128.4 (CHAr), 129.9 (CHAr), 136.9 (CAr), 167.4 (C=O); ν_{max}/cm^{-1} (neat) 3289, 2952, 2929, 2260-2100, 1647 (C=O), 1462, 1427, 1253; m/z (ESI+) 373 ($[M+H]^+$, 100%); HRMS calc. for $C_{21}H_{33}O_2N_2Si$ 373.2306, found 373.2314 $[M+H]^+$.

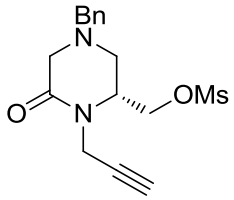
***(R)-4-Benzyl-6-(hydroxymethyl)-1-(prop-2-yn-1-yl)piperazin-2-one* 2.47**



TBAF (350 µL of a 1 M solution in THF, 0.34 mmol) was added to a stirred solution of alkyne **2.46** (77 mg, 0.21 mmol) in THF (1.0 mL) at 0 ºC under nitrogen. After 30 minutes, the reaction was quenched with an aq. sat. solution of NH_4Cl (4 mL), extracted with ethyl acetate (3 × 4 mL) and the combined organic layers dried over $MgSO_4$ and concentrated under reduced pressure affording alcohol **2.47** (47 mg, 89%) as a thick yellow oil.

R_f 0.51 (DCM/MeOH 9:1); $[\alpha]_D^{20}$ = -12.2 (c 8.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 2.24 (t, 1H, *J* 2.6 Hz, C≡CH), 2.64 (ddd, 1H, *J* 1.5, 3.7 and 11.8 Hz, H5), 2.88 (d, 1H, *J* 16.5 Hz, H3), 3.10 (dt, 1H, *J* 1.5 and 11.8 Hz, H5'), 3.43 (dd, 1H, *J* 1.5 and 16.5 Hz, H3'), 3.49 (d, 1H, *J* 12.9 Hz, C*H*H'Ph), 3.53 (d, 1H, *J* 12.9 Hz, CH*H*'Ph), 3.63 (m, 1H, H6), 3.71 (dd, 1H, *J* 2.2 and 11.6 Hz, C*H*H'OH), 3.81 (dd, 1H, *J* 2.5 and 17.7 Hz, NC*H*H'C≡C), 3.87 (ddd, 1H, *J* 1.5 and 4.2 and 11.6 Hz, CH*H*'OH), 4.53 (s, 1H, OH), 4.76 (dd, 1H, *J* 2.6 and 17.7 Hz, NCH*H*'C≡C), 7.16-7.35 (m, 5H, HAr); δ_C (100 MHz, $CDCl_3$): 33.2 (CH_2, NCH_2), 54.4 (CH, C6), 54.4 (CH_2, C5), 57.0 (CH_2, C3), 61.9 (CH_2, CH_2Ph), 64.0 (CH_2, CH_2OH), 72.7 (C≡C), 78.1 (C≡C), 128.1 (CHAr), 128.8 (CHAr), 129.1 (CHAr), 135.6 (CAr), 166.7 (C=O); ν_{max}/cm^{-1} (neat) 3391, 3288, 2910, 2150, 1634 (C=O), 1455, 1427, 1266; m/z (ESI+) 259 ($[M+H]^+$, 100%); HRMS calc. for $C_{15}H_{19}O_2N_2$ 259.1441, found 259.1440 $[M+H]^+$.

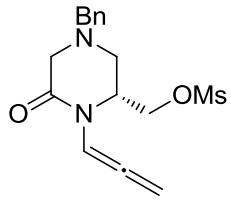
***(R)-(4-Benzyl-6-oxo-1-(prop-2-yn-1-yl)piperazin-2-yl)methyl methanesulfonate* 2.48**



MsCl (16 µL, 24 mg, 0.21 mmol) was added to a stirred solution of alcohol **2.47** (41 mg, 0.16 mmol) and NEt_3 (84 µL, 61 mg, 0.60 mmol) in anhydrous DCM (0.5 mL) at 0 ºC, under nitrogen and the reaction mixture was stirred overnight at rt. The reaction was quenched with an aq. sat. solution of NH_4Cl (3 mL), extracted with ethyl acetate (3 × 3 mL) and the combined organic layers dried over $MgSO_4$ and concentrated under vacuum, to yield mesylate **2.48** as a yellow oil.

R$_f$ 0.31 (ethyl acetate/petroleum ether 1:1); $[\alpha]_D^{20}$ = -8.9 (c 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 2.22 (t, 1H, *J* 2.6 Hz, C≡CH), 2.45 (dd, 1H, *J* 3.4 and 12.2 Hz, H3), 2.83 (s, 3H, CH_3), 2.89 (d, 1H, *J* 16.8 Hz, H5), 2.98 (dt, 1H, *J* 2.0 and 12.2 Hz, H3'), 3.41-3.45 (m, 1H, H5'), 3.44 (d, 1H, *J* 12.8 Hz, C*H*H'Ph), 3.54 (d, 1H, *J* 12.8 Hz, CH*H*'Ph), 3.77-3.82 (m, 1H, H2), 3.91 (dd, 1H, *J* 2.6 and 17.6 Hz, NC*H*H'C≡C), 4.33 (ddd, 1H, *J* 0.6, 4.3 and 9.7 Hz, C*H*H'OMs), 4.41 (dd, 1H, *J* 8.4 and 9.7 Hz, CH*H*'OMs), 4.53 (dd, 1H, *J* 2.6 and 17.6 Hz, NCH*H*'C≡C), 7.17-7.31 (m, 5H, HAr); δ_C (100 MHz, $CDCl_3$): 34.6 (CH_2, NCH_2), 37.3 (CH_3), 50.1 (CH_2, C3), 54.7 (CH, C2), 57.3 (CH_2, C5), 61.4 (CH_2, CH_2Ph), 66.8 (CH_2, CH_2OMs), 73.1 (C, C≡C), 77.9 (CH, C≡CH), 127.8 (CHAr), 128.6 (CHAr), 129.2 (CHAr), 136.5 (CAr), 167.1 (C=O); ν_{max}/cm^{-1} (neat) 3282, 2849, 2811, 1657 (C=O), 1464, 1352, 1341, 1172; m/z (ESI+) 337 ($[M+H]^+$, 50%), 158 (55%), 60 (100%); HRMS calc. for $C_{16}H_{20}O_4N_2S$ 337.1217, found 337.1219 $[M+H]^+$.

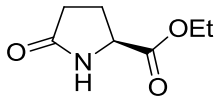
***(R)-(4-Benzyl-6-oxo-1-(propa-1,2-dien-1-yl)piperazin-2-yl)methyl methanesulfonate* 2.49**



A Schlenk tube was purged with argon and charged with LAED (21 mg, 0.21 mmol). DMSO (0.5 mL) was added and the stirred solution was cooled to 0 °C. A solution of mesylate **2.48** (35 mg, 0.10 mmol) in DMSO (0.5 mL) was added dropwise and the mixture was stirred at rt overnight. The reaction mixture was quenched with an aq. sat. solution of NH_4Cl (3 mL), extracted with ethyl acetate (3 × 3 mL) and the combined organic layers dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography (petroleum ether/ethyl acetate 7:3 to 1:1) to afford allene **2.49** (3 mg, 9%) as a yellow oil and recovered starting material **2.48** (6 mg, 18%).

R_f 0.60 (ethyl acetate/petroleum ether 1:1); $[\alpha]_D^{20}$ = -10.6 (c 0.75, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 2.43 (dd, 1H, *J* 2.1 and 12.2 Hz, H3), 2.78 (s, 3H, CH_3), 2.90 (brd, 1H, *J* 17.1 Hz, H5), 3.06 (dd, 1H, *J* 1.6 and 12.2 Hz, H3'), 3.48 (d, 2H, *J* 12.8 Hz, C*H*H'Ph), 3.49 (dd, 1H, *J* 2.0 and 17.1 Hz, H5'), 3.55 (d, 1H, *J* 12.8 Hz, CH*H*'Ph), 3.67-3.77 (m, 1H, H2), 4.22 (ddd, 1H, *J* 1.2, 3.2 and 9.3 Hz, C*H*H'OMs), 4.42 (dd, 1H, *J* 9.3 Hz, CH*H*'OMs), 5.39 (dd, 1H, *J* 6.5 and 10.7 Hz, =C*H*H'), 5.50 (dd, 1H, *J* 6.5 and 10.7 Hz, =CH*H*'), 7.20-7.30 (m, 5H, HAr), 7.38 (t, 1H, *J* 6.5 Hz, =CH); δ_C (100 MHz, $CDCl_3$): 37.1 (CH_3), 49.2 (CH_2, C3), 53.2 (CH, C2), 57.3 (CH_2, C5), 61.4 (CH_2, CH_2Ph), 65.4 (CH_2, CH_2OMs), 89.1 (CH_2, =CHH), 97.1 (CH, =CH), 127.8 (CHAr), 128.6 (CHAr), 129.2 (CHAr), 136.5 (CAr), 165.2 (C=O), 200.8 (C, =C=); ν_{max}/cm^{-1} (neat) 3253, 2924, 1659 (C=O), 1455, 1360, 1347, 1174; m/z (ESI+) 337 ($[M+H]^+$, 100%); HRMS calc. for $C_{16}H_{21}O_4N_2S$ 337.1217, found 337.1217 $[M+H]^+$.

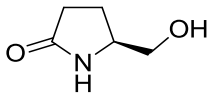
(*S*)-Ethyl 5-oxopyrrolidine-2-carboxylate 2.51



Thionyl chloride (8.0 mL, 13.2 g, 0.11 mmol) was added dropwise to a stirred solution of L-glutamic acid **2.50** (8 g, 40.8 mmol) in ethanol (100 mL), at 0 ºC under nitrogen. The resulting mixture was stirring for two hours at 0 ºC then heated to reflux for an additional two hours. The reaction mixture was concentrated under vacuum and the residue purified by flash column chromatography (DCM/MeOH 1:0-19:1) to yield **2.51** (5.6 g, 90%) as a white solid.

R_f 0.74 (1:9 MeOH/DCM); mp = 53 ºC, [lit.[184] 49-51 ºC]; $[\alpha]_D^{20}$ = +7.5 (c 5.0, ethanol), [lit.[184] $[\alpha]_D^{20}$ = +2.4 (c 1.0, ethanol)]; δ_H (600 MHz, $CDCl_3$): 1.32 (t, 3H, *J* 7.1 Hz, CH_3), 2.23-2.30 (m, 1H, H3), 2.36-2.42 (m, 2H, H3', H4), 2.44-2.51 (m, 1H, H4'), 4.22-4.29 (m, 1H, H2), 4.25 (q, 1H, *J* 7.1 Hz, OCH_2), 6.26 (s, 1H, NH). Data in agreement with literature.[184]

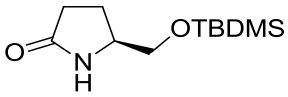
***(S)-5-(Hydroxymethyl)pyrrolidin-2-one* 2.52**



Using the procedure of Ackermann and co-workers:[185] $NaBH_4$ (335 mg, 8.90 mmol) was added to a stirred solution of ester **2.51** (1.4 g, 8.90 mmol) in ethanol (5 mL) of at 0 ºC, under nitrogen. After 2 h, the pH of the solution was adjusted to 4 by addition of conc. HCl. The reaction mixture was concentrated under vacuum and the residue suspended in DCM. The suspension was filtered through Celite® and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography (MeOH/DCM 2:23) to yield alcohol **2.52** (860 mg, 86%) as a white solid.

R_f 0.46 (1:9 MeOH/DCM); mp = 84-87 ºC, [lit.[186] 86-87 ºC]; $[\alpha]_D^{20}$ = +29.2 (c 5.0, ethanol), [lit.[187] $[\alpha]_D^{20}$ = +31.5 (c 1.0, ethanol)]; δ_H (600 MHz, $CDCl_3$): 1.75-1.81 (m, 1H, H4), 2.12-2.18 (m, 1H, H4'), 2.29-2.39 (m, 2H, H3, H3'), 3.44 (td, 1H, *J* 6.8 and 11.5 Hz, C*H*H'OH), 3.66 (m, 1H, *J* 3.0, 5.7 and 11.5 Hz, CH*H*'OH), 3.77-3.81 (m, 1H, H5), 4.36 (brt, 1H, *J* 5.9 Hz, OH), 7.40 (s, 1H, NH); δ_C (150 MHz, $CDCl_3$): 22.7 (CH_2, C4), 30.4 (CH_2, C3), 56.6 (CH, C5), 66.0 (CH_2, CH_2OH), 179.5 (C=O); m/z (ES+) 116 ($[M+H]^+$, 100%). Data in agreement with literature.[187]

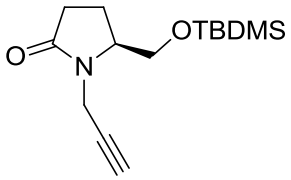
(*S*)-5-(((*Tert*-butyldimethylsilyl)oxy)methyl)pyrrolidin-2-one 2.53



TBDMSCl (1.8 g, 12.20 mmol) was added to a stirred solution of alcohol **2.52** (1.3 g, 10.20 mmol) and imidazole (1.0 g, 15.30 mmol) in anhydrous acetonitrile (20 mL) at room temperature, under nitrogen. The reaction mixture was stirred overnight and then quenched with water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to yield the protected alcohol **2.53** (quantitative) as a pale yellow oil which required no further purification.

R_f 0.28 (ethyl acetate); $[\alpha]_D^{20}$ = +41.6 (c 11.2, ethanol), [lit.[188] $[\alpha]_D^{20}$ = +44.7 (c 1.8, ethanol)]; δ_H (600 MHz, $CDCl_3$): 0.05 (s, 3H, CH_3), 0.05 (s, 3H, CH_3), 0.88 (s, 9H, *t*-Bu), 1.70-176 (m, 1H, H4), 2.14-2.19 (m, 1H, H4'), 2.29-2.39 (m, 2H, H3/H3'), 3.43 (dd, 1H, *J* 3.9 and 10.1 Hz, C*H*H'OTBDMS), 3.62 (dd, 1H, *J* 7.8 and 10.1 Hz, CH*H*'OTBDMS'), 3.72- 3.78 (m, 1H, H5), 5.87 (s, 1H, NH); δ_C (150 MHz, $CDCl_3$): -5.3 (CH3), -5.3 (CH_3), 18.3 (C), 22.8 (CH_2, C4), 25.9 (CH_3), 29.9 (CH_2, C3), 55.9 (CH, C5), 67.1 (CH_2, CH_2OTBDMS), 178.0 (C=O). Data in agreement with literature.[188]

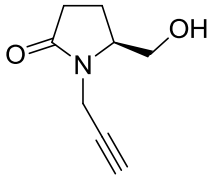
(*S*)-5-(((*Tert*-butyldimethylsilyl)oxy)methyl)-1-(prop-2-yn-1-yl)pyrrolidin-2-one 2.54



NaH (329 mg of a 60% suspension in mineral oil, 13.70 mmol) was added portionwise to a stirred solution of protected alcohol **2.53** (2.6 g, 11.40 mmol) in anhydrous THF (13 mL) at room temperature, under nitrogen. After 30 minutes propargyl bromide **2.9** (2.7 mL of an 80% solution in toluene, 0.24 mmol) was added and the reaction mixture was stirred for 21 h. After that time the reaction was quenched with an aq. sat. solution of NH_4Cl (15 mL), extracted with ethyl acetate (3 × 15 mL) and the combined organic layers dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate/petroleum ether 1:1) to afford alkyne **2.54** (2.4 g, 80%) as a yellow oil.

R_f 0.72 (ethyl acetate); $[\alpha]_D^{20}$ = +4.0 (c 1.5, $CHCl_3$), [lit.[189] $[\alpha]_D^{20}$ =+2.53 (c 1.8, $CHCl_3$)] ; δ_H (600 MHz, $CDCl_3$): 0.05 (s, 3H, CH_3), 0.06 (s, 3H, CH_3), 0.88 (s, 9H, *t*-Bu), 1.84-1.89 (m, 1H, H4), 2.08-2.15 (m, 1H, H4'), 2.19 (t, 1H, *J* 2.5 Hz, C≡CH), 2.33 (ddd, 1H, *J* 5.0, 10.2 and 17.5 Hz, H3), 2.43-2.49 (m, 1H, H3'), 3.63 (dd, 1H, *J* 3.9 and 10.8 Hz, C*H*H'OTBDMS), 3.72 (ddd, 1H, *J* 1.0, 2.5 and 17.6 Hz, NC*H*H'C≡C), 3.78 (dd, 1H, *J* 3.9 and 10.8 Hz, CH*H*'OTBDMS), 3.88 (dq, 1H, *J* 3.9 and 7.9 Hz, H5), 4.60 (dd, 1H, *J* 2.6 and 17.6 Hz, NCH*H*'C≡C); δ_C (150 MHz, $CDCl_3$): -5.4 (CH_3), -5.4 (CH_3), 18.2 (C), 21.3 (CH_2), 25.9 (CH_3), 30.4 (CH_2), 30.6 (CH_2), 58.4 (CH, C5), 63.8 (CH_2), 72.0 (CH, C≡C), 78.3 (CH, C≡CH), 175.1 (C=O). Data in agreement with literature.[189]

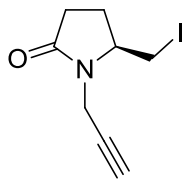
***(S)-5-(Hydroxymethyl)-1-(prop-2-yn-1-yl)pyrrolidin-2-one* 2.55**



TBAF (15.2 mL of a 1 M solution in THF, 15.20 mmol) was added to a stirred solution of alkyne **2.54** (2.4 g, 9.10 mmol) in anhydrous THF (20 mL) at 0 ºC, under nitrogen. The reaction mixture was stirred for 30 min and then quenched with an aq. sat. solution of NH_4Cl (20 mL), extracted with ethyl acetate (3 × 20 mL) and the combined organic layers dried over $MgSO_4$ and concentrated under reduced pressure affording alcohol **2.55** (3.6 g, quant.) as a yellowish solid.

R_f 0.44 (1:9 MeOH/DCM); mp: 50-54 ºC; $[\alpha]_D^{20}$ = +15.0 (c 5.0, $CHCl_3$); δ_H (600 MHz, $CDCl_3$): 1.96-2.06 (m, 1H, H4), 2.09-2.21 (m, 1H, H4'), 2.26 (t, 1H, *J* = 2.5 Hz, C≡CH), 2.31-2.40 (m, 1H, H3), 2.46-2.55 (m, 1H, H3'), 2.58 (brs, 1H, OH), 3.65 (brd, 1H, *J* 11.8 Hz, C*H*H'OH), 3.80-3.89 (m, 1H, H5), 3.98 (brd, 1H, *J* = 11.8 Hz, CH*H*'OH), 4.05 (dd, 1H, *J* = 17.6, 2.3 Hz, NC*H*H'C≡C), 4.31 (dd, 1H, *J* = 17.6, 2.4 Hz, NCH*H*'C≡C); δ_C (150 MHz, $CDCl_3$): 20.8 (CH_2, C4), 30.3 (CH_2, C3), 30.6 (CH_2, NCH_2), 59.3 (CH, C5), 62.7 (CH_2, CH_2OH), 72.0 (C, C≡C), 78.4 (CH, C≡CH), 175.7 (C=O). ν_{max}/cm^{-1} (neat) 3346, 3275, 2931, 2874, 1650 (C=O), 1450, 1418, 1430, 1247; m/z (ES+) 154 ($[M+H]^+$,100%); HRMS calc. for $C_8H_{12}O_2N$ 154.0863, found 154.0861 $[M+H]^+$.

***(S)-5-(Iodomethyl)-1-(prop-2-yn-1-yl)pyrrolidin-2-one* 2.56**

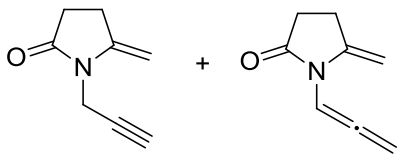


MsCl (92 μL, 136 mg, 1.19 mmol) was added to a stirred solution of alcohol **2.55** (141 mg, 0.92 mmol) and NEt_3 (486 μL, 353 mg, 3.48 mmol) in anhydrous DCM (5.0 mL) at rt under argon and the reaction mixture stirred for 18 h. The reaction was quenched with water (5 mL) and the layers separated. The

aqueous phase was extracted with ethyl acetate (3 × 5 mL), dried over $MgSO_4$ and concentrated under vacuum to give the corresponding mesylate (212 mg, 0.92 mmol) that was used without further purification. The mesylate was dissolved in stirred anhydrous MeCN (2.0 mL), sodium iodide (413 mg, 2.78 mmol) was added and the reaction mixture was heated to reflux overnight. After evaporation of the solvent, the residue was purified by flash column chromatography (ethyl acetate/petroleum ether 1:1 to 4:2) affording iodide **2.56** (199 mg, 83%) as a clear oil.

R_f 0.74 (1:9 MeOH/DCM); $[\alpha]_D^{20}$ = -29.4 (c 8.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.74-1.88 (m, 1H, H4), 2.16- 2.31 (m, 2H, H4'), 2.24 (t, 1H, *J* 2.4 Hz, C≡CH), 2.38 (ddd, 1H, *J* 6.2, 10.4, 17.0 Hz, H3), 2.55 (ddd, 1H, *J* 6.0, 10.4, 17.0 Hz, H3'), 3.38 (dd, 1H, *J* 5.9 and 10.8 Hz, C*H*H'I), 3.45 (dd, 1H, *J* 2.5 and 10.8 Hz, CH*H*'I), 3.64 (td, 1H, *J* 2.3 and 17.9 Hz, NC*H*H'C≡C), 3.78-3.83 (m, 1H, H5), 4.60 (dd, 1H, *J* 2.4 and 17.9 Hz, NCH*H*'C≡C); δ_C (100 MHz, $CDCl_3$): 10.8 (CH_2, CH_2I), 24.7 (CH_2, C4), 29.8 (CH_2, C3), 30.0 (CH_2, NCH_2), 56.3 (C5), 72.9 (C, C≡C), 77.2 (CH, C≡CH), 174.4 (C=O); ν_{max}/cm^{-1} (neat) 3287, 3233, 2952, 2116, 1677 (C=O), 1409, 1247. NMR in agreement with literature – data for the racemic compound.[190]

***5-Methylene-1-(prop-2-yn-1-yl)pyrrolidin-2-one* 2.57 *and* 5-methylene-1-(propa-1,2-dien-1-yl)pyrrolidin-2-one 2.58**



2.57 **2.58**

A Schlenk tube was charged with LAED (35 mg, 0.38 mmol) and purged with argon. DMSO (0.5 mL) was added and the stirred solution was cooled to 0 °C. A solution of iodide **2.56** (50 mg, 0.19 mmol) in DMSO (0.5 mL) was added dropwise and the mixture was stirred at rt overnight. The reaction mixture was quenched with an aq. sat. solution of NH_4Cl (3 mL), extracted with ethyl acetate (3 × 3 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash

column chromatography (petroleum ether/ethyl acetate 9:1) afforded allene **2.58** (5 mg, 18%) and alkyne **2.57** (18 mg, 72%) as yellow oils.

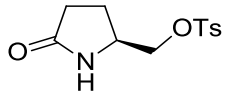
***5-Methylene-1-(propa-1,2-dien-1-yl)pyrrolidin-2-one* 2.58**

R_f 0.74 (ethyl acetate/petroleum ether 1:1); δ_H (400 MHz, $CDCl_3$): 2.50- 2.54 (m, 2H, H3), 2.78-2.66 (m, 2H, H4), 4.31 (d, 1H, *J* 1.7 Hz, =C*H*H'), 4.93 (d, 1H, *J* 1.7 Hz, =CH*H*'), 5.41 (d, 2H, *J* 6.7 Hz, $=CH_2$), 6.93 (t, 1H, *J* 6.7 Hz, =CH); δ_C (100 MHz, $CDCl_3$): 24.3 (CH_2, C4), 26.5 (CH_2, C3), 28.6 (CH_2, $=CH_2$), 85.8 (CH_2, =CHH), 88.7 (CH, =CH), 204.1 (C, =C=); ν_{max}/cm^{-1} (neat) 3299, 2923, 2846, 1681 (C=O), 1365; m/z (ES+) 136 ($[M+H]^+$, 100%); HRMS calc. for $C_8H_{10}ON$ 136.0757, found 136.0753 $[M+H]^+$.

***5-Methylene-1-(prop-2-yn-1-yl)pyrrolidin-2-one* 2.57**

R_f 0.58 (ethyl acetate/petroleum ether 1:1); δ_H (400 MHz, $CDCl_3$): 2.18 (t, 1H, *J* 2.5 Hz, C≡CH), 2.49-2.55 (m, 2H, H3,H3'), 2.69-2.76 (m, 2H, H4,H4'), 4.26-4.28 (m, 3H, =CHH'/NCHH'C≡C), 4.42 (br q, 1H, *J* 2.0 Hz, =CHH'); δ_C (100 MHz, $CDCl_3$): 23.6 (CH_2, C4), 29.0 (CH_2), 29.1 (CH_2), 71.4 (C, C≡C), (CH, C≡CH) 85.6 (CH_2, $=CH_2$), 145.2 (CH, C5), 175.0 (C=O); ν_{max}/cm^{-1} (neat) 3357, 3285, 2983, 2932, 1664 (C=O), 1437, 1405; m/z (ES+) 136 ($[M+H]^+$, 100%); HRMS calc. for $C_8H_{10}ON$ 136.0757, found 136.0756 $[M+H]^+$.

(*S*)-(5-Oxopyrrolidin-2-yl)methyl 4-methylbenzenesulfonate 2.59

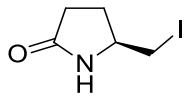


TsCl (1.5 g, 7.92 mmol) was added to a stirred solution of alcohol **2.52** (766 mg, 6.65 mmol) and NEt_3 (1.8 mL, 1.3 g, 13.20 mmol) in anhydrous DCM (20 mL) at rt under nitrogen. DMAP (81 mg, 0.66 mmol) was added and the reaction mixture was stirred overnight. The solvent was evaporated under vacuum and the residue purified by flash column chromatography (petroleum ether/ethyl acetate 2:4) to yield tosylate **2.59** (1.8 g, 98%) as an off-white solid.

R_f 0.65 (MeOH/DCM 1:19); mp = 126 ºC [lit.[191] 124-127 ºC]; $[\alpha]_D^{20}$ = +27.4 (c 3.6, $CHCl_3$), [lit.[191] $[\alpha]_D^{20}$ = +20.3 (c 1.0, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$): 1.68-1.80 (m,

1H, H3), 2.13-2.21 (m, 1H, H3'), 2.36-2.22 (m, 2H, H4/H4'), 2.40 (s, 3H, CH_3), 3.80-3.91 (m, 2H, H2/C*H*H'OTs), 3.92-4.04 (m, 1H, CH*H*'OTs), 6.95 (s, 1H, NH), 7.32 (d, 2H, *J* 8.2 Hz, HAr), 7.74 (d, 2H, *J* 8.2 Hz, HAr); δ_C (100 MHz, $CDCl_3$): 21.7 (CH_3), 22.8 (CH_2, C3), 29.4 (CH_2, C4), 52.6 (CH, C2), 72.0 (CH_2, CH_2OTs), 127.9 (CHAr), 130.1 (CHAr), 132.2 (CAr), 145.4 (CAr), 178.3 (C=O); m/z (ES+) 270 ($[M+H]^+$, 100%). Consistent with literature data.[191]

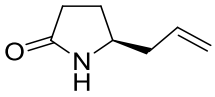
(*S*)-5-(Iodomethyl)pyrrolidin-2-one 2.60



NaI (3.5 g, 23.1 mmol) was added to a stirred solution of tosylate **2.59** (1.8 g, 6.62 mmol) in anhydrous acetonitrile (36 mL) under N_2 and the reaction mixture was heated at reflux for 5 h. After cooling to rt, the precipitate formed was filtered off and the filtrate was concentrated under vacuum. The residue was dissolved in DCM, washed with an aq. sat. solution of $Na_2S_2O_3$ and the organic layer dried over $MgSO_4$. After concentration under reduced pressure, iodolactam **2.60** was obtained quantitatively as a yellowish solid.

R_f 0.28 (MeOH/DCM 1:19), mp = 78-81 ºC [lit.[115] 79-81 ºC]; $[\alpha]_D^{20}$ = -10.0 (c 6.6, $CHCl_3$), [lit.[115] $[\alpha]_D^{20}$ = -11.6 (c 1.1, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$): 1.71-1.83 (m, 1H, H4), 2.23-2.28 (m, 1H, H4'), 2.35-2.29 (m, 1H, H3), 2.35-2.49 (m, 1H, H3'), 3.16 (dd, 1H, *J* 4.4 and 8.5 Hz, C*H*H'I), 3.19 (dd, 1H, *J* 4.4 and 8.5 Hz, CH*H*'I), 3.79 (dq, 1H, *J* 5.9 Hz, H5), 6.97 (s, 1H, NH); δ_C (100 MHz, $CDCl_3$): 9.6 (CH_2, CH_2I), 25.4 (CH_2, C4), 28.4 (CH_2, C3), 53.2 (CH, C5), 176.4 (C=O). Data in agreement with literature.[115]

(*S*)-5-Allylpyrrolidin-2-one 2.63

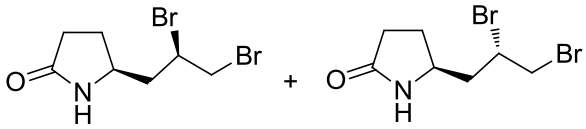


Using the procedure of Kamimura and co-workers:[115] Vinylmagnesium bromide **2.62** (7.6 mL of a 1 M solution in THF, 7.60 mmol) was added to a stirred

solution of iodolactam **2.60** (300 mg, 1.33 mmol) and CuI (660 mg, 3.47 mmol) in anhydrous THF (10 mL) at -30 ºC, under argon. The reaction mixture was stirred for 2 h at -30 ºC, then was allowed to warm to 4 ºC and stirred overnight at 4 ºC. The reaction was quenched with an aq. sat. solution of NH_4Cl (10 mL), the layers separated and the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (petroleum ether/ethyl acetate 9:1 to 0:1) to yield alkene **2.63** (124 mg, 74%) as a brown oil.

R_f 0.28 (ethyl acetate); $[\alpha]_D^{20}$ = +3.6 (c 2.2, $CHCl_3$), [lit.[192] $[\alpha]_D^{20}$ = +2.5 (c 1.2, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$): 1.68-1.80 (m, 1H, H4), 2.15-2.28 (m, 3H, H4'/CCHH'), 2.29-2.34 (m, 2H, H3/H3'), 3.69 (dq, 1H, *J* 6.6 Hz, H5), 5.06-5.17 (m, 2H, =CHH'), 5.68-5.81 (m, 1H, =CH), 6.62 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$): 26.6 (CH_2, C4), 30.3 (CH_2, C3), 41.0 (CH_2, CCH_2), 53.8 (CH, C5), 118.4 (CH_2, $=CH_2$), 133.7 (CH, =CH), 178.3 (C=O). Data in agreement with literature.[115]

***(5S)-5-(2,3-Dibromopropyl)pyrrolidin-2-one* 2.64a/b**



Br_2 (205 μL, 639 mg , 3.98 mmol) was added dropwise to a stirred solution of alkene **2.63** (250 mg, 2.00 mmol) in anhydrous DCM (5.0 mL) at 0 ºC under argon and the reaction mixture stirred for 30 minutes. The reaction mixture was diluted with ethyl acetate and quenched with an aq. sat. solution of $Na_2S_2O_3$. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic layers were dried over $MgSO_4$, concentrated under vacuum yielding dibromoalkane **2.64a/b** (570 mg, 67%) as a white solid comprising a mixture of two isomers. The isomers were separated by flash column chromatography (petroleum ether/ethyl acetate 1:1 to 0:1) to provide analytical samples as colourless oils.

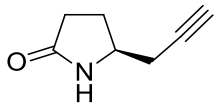
***Less polar isomer:* 2.64a**

R_f 0.31 (ethyl acetate); $[\alpha]_D^{20}$ = +53.8 (c 6.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.75-1.86 (m, 1H, C*H*H'Br), 1.881.95 (m, 1H, H4), 2.24-2.46 (m, 4H, CH*H*'Br/H3'/H3/H4'), 3.61 (dd, 1H, *J* 10.0 and 10.3 Hz, C*H*H'), 3.90 (dd, 1H, *J* 4.1 and 10.3 Hz, CH*H*'), 3.95-4.03 (m, 1H, CHBr), 4.18-4.28 (m, 1H, H5), 7.16 (s, 1H, NH); δ_C (100 MHz, $CDCl_3$): 27.3 (CH_2, CH_2Br), 29.9 (CH_2, C3), 36.3 (CH_2, CHH), 43.3 (CH_2, C4), 49.1 (CH, C5), 52.5 (CH, CHBr), 178.67 (C=O). ν_{max}/cm^{-1} (neat) 3167, 3079, 2964, 2888, 1680 (C=O), 1433, 1392, 1355, 1316, 1298, 1266; m/z (ES+) 284 ($[M+H]^+$, 51% $C_7H_{12}{}^{79}Br_2NO$), 286 ($[M+H]^+$, 100% $C_7H_{12}{}^{79}Br^{81}BrNO$), 288 ($[M+H]^+$, 49% $C_7H_{12}{}^{81}Br_2NO$); HRMS calc. for $C_7H_{12}ON^{79}Br_2$ 283.9280, found 283.9283 $[M+H]^+$.

***More polar isomer:* 2.64b**

R_f 0.18 (ethyl acetate); $[\alpha]_D^{20}$ = -29.2 (c 6.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.66-1.80 (m, 1H, C*H*H'Br), 1.96-2.11 (m, 1H, H4), 2.27-2.48 (m, 4H, H4/H3/H3'/CH*H*'Br), 3.61 (dd, 1H, *J* 10.3 Hz, C*H*H'), 3.88 (dd, 1H, *J* 4.1 and 10.3 Hz, CH*H*'), 3.88-3.95 (m, 1H,CHBr), 4.11 (tt, 1H, *J* 4.1 and 10.3 Hz, H5), 6.55 (s, 1H, NH); δ_C (100 MHz, $CDCl_3$): 27.0 (CH_2, CH_2Br), 29.8 (CH_2, C3), 36.1 (CH_2, CHH), 42.9 (CH_2, C4), 48.2 (CH, C5), 53.1 (CH, CHBr), 177.9 (C=O); ν_{max}/cm^{-1} (neat) 3284, 3188, 3094, 2940, 1647 (C=O), 1272, 1150; m/z (ES+) 284 ($[M+H]^+$, 51% $C_7H_{12}{}^{79}Br_2NO$), 286 ($[M+H]^+$, 100% $C_7H_{12}{}^{79}Br^{81}BrNO$), 288 ($[M+H]^+$, 49% $C_7H_{12}{}^{81}Br_2NO$); HRMS calc. for $C_7H_{12}ON^{79}Br_2$ 283.9280, found 283.9285 $[M+H]^+$.

***(S)-5-(Prop-2-yn-1-yl)pyrrolidin-2-one* 2.61**

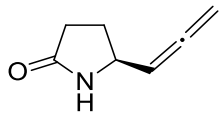


KO^{t}Bu (132 mg, 0.59 mmol) was added in small portions to a stirred solution of dibromoalkane **2.64a/b** (71 mg, 0.14 mmol) in anhydrous THF (2.0 mL) at rt under argon. After 24 h, the solvent was removed under vacuum and the residue was purified by flash column chromatography (petroleum ether/ethyl

acetate 1:1 to 0:1) affording the desired alkyne **2.61** (8 mg, 25%), allene **2.65** (2 mg, 8%) and alkyne **2.66** (3 mg, 10%) as yellow oils.

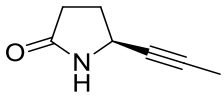
R_f 0.23 (Ethyl acetate 2 elutions); mp = 104-106 ºC, [lit.[128] (racemate) 109-111 ºC]; $[\alpha]_D^{20}$ = +66.4 (c 1.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.77-1.94 (m, 1H, H4), 2.04 (t, 1H, *J* 2.6 Hz, C≡CH), 2.26-2.48 (m, 5H, H4'/H3/H3'/CHH'), 3.77-3.88 (dq, 1H, *J* 6.2 Hz, H5), 6.05 (s, 1H, NH); δ_C (100 MHz, $CDCl_3$): 26.3 (CH_2, C4), 26.3 (CH_2), 29.9 (CH_2), 51.0 (CH, C5), 70.9 (CH, C≡CH), 79.9 (C, C≡C), 177.8 (C=O). Data in agreement with literature (racemic compound).[128]

***(S)-5-(Propa-1,2-dien-1-yl)pyrrolidin-2-one* 2.65**



R_f 0.32 (Ethyl acetate 2 elutions); $[\alpha]_D^{20}$ = +52.0 (c 0.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.90-1.99 (m, 1H, H4), 2.26-2.50 (m, 3H, H4'/H3/H3'), 4.19-4.21 (m, 1H, H5), 4.88 (dd, 1H, *J* 2.1 and 6.5 Hz, =C*H*H'), 4.88 (dd, 1H, *J* 2.1 and 6.5 Hz, =CH*H*'), 5.16 (ddd, 1H, *J* 6.5 Hz, =CH), 5.63 (s, 1H, NH); δ_C (100 MHz, $CDCl_3$): 28.4 (CH_2), 29.7 (CH_2), 52.8 (CH, C5), 78.3 (CH_2, $=CH_2$), 92.8 (CH, =CH), 178.0 (C=O), 207.4 (=C=). Data in agreement with literature (racemic compound).[193]

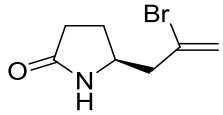
***(S)-5-(Prop-1-yn-1-yl)pyrrolidin-2-one* 2.66**



R_f 0.37 (Ethyl acetate 2 elutions); $[\alpha]_D^{20}$ = +7.5 (c 0.8, $CHCl_3$) ; δ_H (400 MHz, $CDCl_3$): 1.82 (d, 3H, *J* 2.2 Hz, CH_3), 2.07-2.18 (m, 1H, H4), 2.22-2.34 (m, 1H, H3), 2.35-2.51 (m, 1H, H3'/H4'), 4.33 (ddd, 1H, *J* 2.2, 5.4 and 7.4 Hz, H5), 5.76 (s, 1H, NH); δ_C (100 MHz, $CDCl_3$): 3.5 (CH_3), 29.3 (CH_2), 29.5 (CH_2), 44.9 (CH, C5), 78.2 (C≡C), 80.3 (C≡C), 177.4 (C=O). Data in agreement with literature (racemic compound).[194]

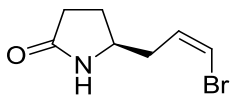
***(S)-5-(2-Bromoallyl)pyrrolidin-2-one* 2.67**

K^{t}BuO (113 mg, 1.01 mmol) was added to a stirred solution of dibromoalkanes **2.64a/b** (115 mg, 0.40 mmol) in anhydrous THF (4.0 mL) at rt, under argon. After 2.5 h, the solvent was removed under vacuum and the residue was purified by flash column chromatography (petroleum ether/ethyl acetate 1:1 to 0:1) to yield alkyne **2.61** (27 mg, 40%), bromoalkene **2.67** (18 mg, 22%) and bromoalkene **2.68** (12 mg, 14%) yellow oils.



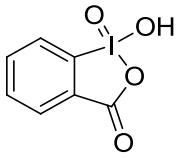
R_f 0.30 (Ethyl acetate 2 elutions); $[\alpha]_D^{20}$ = +49.3 (c 7.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.67-1.81 (m, 1H, H4), 2.28-2.39 (m, 3H, H4'/H3/H3'), 2.57 (dd, 2H, *J* 0.8 and 7.0 Hz, CHH'), 3.93-4.03 (m, 1H, H5), 5.53 (d, 1H, *J* 1.8 Hz, =C*H*H'), 5.67-5.68 (m, 1H, =CH*H*'), 6.24 (s, 1H, NH); δ_C (100 MHz, $CDCl_3$): 26.4 (CH_2, C4), 29.9 (CH_2, C3), 48.3 (CH_2), 52.3 (CH, C5), 119.9 (CH_2, $=CH_2$), 129.4 (C, =CBr), 177.8 (C=O); ν_{max}/cm^{-1} (neat) 3279, 2953, 2865, 1632 (C=O), 1441, 1399, 1266; m/z (ESI) 206 ([M+H]$^+$, 100% $C_7H_{11}{}^{81}BrNO$), 204 ([M+H]$^+$, 98% $C_7H_{11}{}^{81}BrNO$); HRMS calc. for $C_7H_{11}ONBr$ 204.0019, found 204.0020 [M+H]$^+$.

***(S,Z)-5-(3-Bromoallyl)pyrrolidin-2-one* 2.68**



R_f 0.23 (Ethyl acetate 2 elutions); $[\alpha]_D^{20}$ = +57.2 (c 5.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.67-1.79 (m, 1H, H4), 2.18-2.28 (m, 5H, H4'/H3/H3'/CHH'), 3.70 (dq, 1H, *J* 6.5 Hz, H5), 6.07-6.20 (m, 2H, CH=CH), 6.74 (s, 1H, NH); δ_C (100 MHz, $CDCl_3$): 26.3 (CH_2, C4), 30.0 (CH_2, C3), 39.8 (CH_2), 53.2 (CH, C5), 107.8 (CH, =CH), 132.8 (CH, =CH), 178.2 (C=O); ν_{max}/cm^{-1} (neat) 3170, 2920, 2876, 1669 (C=O), 1400, 1375, 1234; m/z (ES+) 206 (100% $C_{12}H_{15}BrN_2O$, ^{79}Br), 204 (98% $C_{12}H_{15}BrN_2O$, ^{81}Br) [M]$^+$. The sample decomposed before HRMS could be obtained.

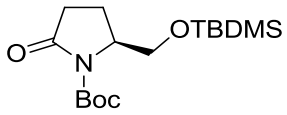
2-Iodoxybenzoic acid



Using the procedure of Frigerio and co-workers:[195] 2-iodobenzoic acid (15 g, 60.48 mmol) was added to a stirred suspension of Oxone™ (55 g, 181.4 mmol) in water (170 mL) and stirred for 10 min. The mixture was then warmed to 70 ºC over 20 min and stirred for 3 h. A further 3 equivalents of Oxone™ (55 g, 181.4 mmol) were added and the reaction stirred for further 3 h. The reaction mixture was cooled to 0 ºC and slowly stirred for 1.5 h, to precipitate the product. The resulting white solid was filtered, washed with water (5 × 10 mL) and acetone (2 × 10 mL) and dried under vacuum at rt for 16 h to yield IBX (13.3 g, 79%) as a white solid.

δ_H (400 MHz, DMSO): 7.85 (dt, 1H, *J* 0.9 and 7,6 Hz, HAr), 7.98-8.05 (m, 2H, HAr), 8.15 (d, 1H, *J* 6.6 Hz, HAr). NMR in agreement with literature.[195]

(*S*)-*Tert*-butyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-5-oxopyrrolidine-1-carboxylate 2.75

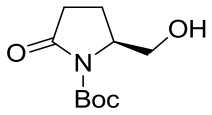


DMAP (234 mg, 1.92 mmol) was added to a stirred solution of amide **2.53** (4.4 g, 19.27 mmol), triethylamine (8.1 mL, 5.9 g, 57.80 mmol) and Boc_2O (6.3 g, 28.90 mmol) in DCM (88 mL) at 0 ºC under nitrogen. The reaction was stirred overnight and then quenched with water (50 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to yield the product **2.75** (4.7 g, 70%) as a yellow oil.

R_f 0.4 (petroleum ether/ethyl acetate 4:1); $[\alpha]_D^{20}$ = -57.7 (c 7.2, $CHCl_3$), [lit.[196] $[\alpha]_D^{20}$ = -61.0 (c 1.1, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$): 0.02 (s, 3H, CH_3), 0.03 (s, 3H, CH_3), 0.86 (s, 9H, CH_3), 1.51 (s, 9H, CH_3), 1.97-2.17 (m, 2H, H3/H3'), 2.35 (ddd, 1H, *J* 2.3, 9.7 and 17.5 Hz, H4), 2.64-2.73 (m, 1H, H4'), 3.67 (dd, 1H, *J*

2.3 and 10.4 Hz, C*H*H'OTBDMS), 3.90 (dd, 1H, *J* 4.0, 10.4 Hz, CH*H*'OTBDMS), 4.13-4.17 (m, 1H, H2); δ_C (100 MHz, $CDCl_3$): -5.6 (CH_3), -5.5 (CH_3), 18.2 (C), 21.1 (CH_2, C3), 25.8 (CH_3), 28.1 (CH_3), 32.3 (CH_2, C4), 58.9 (CH, C2), 64.3 (CH_2, CH_2OTBS), 82.7 (C), 150.1 (C=O), 174.9 (C=O). NMR in agreement with literature.[196]

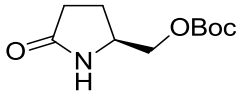
(*S*)-*Tert*-butyl 2-(hydroxymethyl)-5-oxopyrrolidine-1-carboxylate 2.76



Acetic acid (1.4 mL, 1.5 g, 24.90 mmol) was added to a stirred solution of Boc protected amide **2.75** (3.7 g, 11.35 mmol) in THF (74 mL) at room temperature under nitrogen. TBAF (13.6 mL of a 1 M solution in THF, 13.62 mmol) was added dropwise and the reaction stirred overnight. The reaction was then quenched with water (80 mL), the layers separated and the aqueous layer was extracted with ethyl acetate (3 $\times$ 80 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography (petroleum ether/ethyl acetate 1:1) to yield product **2.76** (2.2 g, 88%) as a white solid.

R_f 0.35 (ethyl acetate/petroleum ether 4:1); mp = 98-101 ºC [lit.[197] 98-99 ºC]; $[\alpha]_D^{20}$ = -70.6 (c 5.2, $CHCl_3$), [lit.[197] $[\alpha]_D^{20}$ = -63.0 (c 0.6, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$): 1.50 (s, 9H, CH_3), 1.93-2.02 (m, 1H, H3), 2.10-2.17 (m, 1H, H3'), 2.39 (ddd, 1H, *J* 3.0, 9.9 and 17.7 Hz, H4), 2.63-2.72 (m, 1H, H4'), 2.78 (brs, 1H, OH), 3.71 (dd, 1H, *J* 3.8 and 11.4 Hz, C*H*H'OH), 3.83 (dd, 1H, *J* 4.0, 11.4 Hz, CH*H*'OH), 4.18-4.23 (m, 1H, H2); δ_C (100 MHz, $CDCl_3$): 20.9 (CH_2, C3), 28.0 (CH_3), 32.0 (CH_2, C4), 59.4 (CH, C2), 64.4 (CH_2, CH_2OH), 83.3 (C), 150.7 (C=O), 175.0 (C=O). Data in agreement with literature.[120]

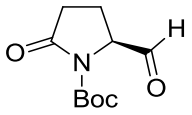
(*S*)-*tert*-Butyl ((5-oxopyrrolidin-2-yl)methyl) carbonate 2.77



TBAF (306 μL of a 1 M solution in THF, 0.34 mmol) was added to a stirred solution of diprotected compound **2.75** (112 mg, 0.34 mmol) in THF (1.0 mL) at room temperature under nitrogen. After 30 minutes the reaction was diluted with ethyl acetate (3 mL) and water was added (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography (petroleum ether/ethyl acetate 1:1 to 0:1) to yield alcohol **2.77** (26 mg, 35%) as a clear oil and amide **2.76** in (15 mg, 21%) as white solid.

R_f 0.25 (ethyl acetate); $[\alpha]_D^{20}$ = +40.2 (c 7.8, $CHCl_3$), [lit.[198] $[\alpha]_D^{20}$ = -63.0 (c 0.6, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$): 1.48 (s, 9H, CH_3), 1.79-1.86 (m, 1H, H3), 2.21-2.30 (m, 1H, H3'), 2.32-2.41 (m, 2H, H4/H4'), 3.87-3.94 (m, 2H, H2/C*H*H'OBoc), 4.10-4.17 (m, 1H, CH*H*'OBoc), 5.99 (s, 1H, NH); δ_C (100 MHz, $CDCl_3$): 23.1 (CH_2, C3), 27.7 (CH_3), 29.3 (CH_2, C4), 52.7 (CH, C2), 69.4 (CH_2, CH_2OBoc), 82.9 (C), 153.2 (C=O), 177.7 (C=O). Data in agreement with literature.[120]

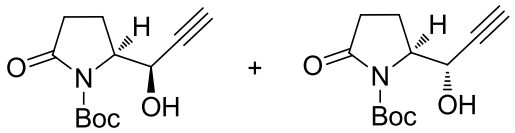
(*S*)-*tert*-Butyl 2-formyl-5-oxopyrrolidine-1-carboxylate 2.78



TEMPO (150 mg, 0.96 mmol) was added to a stirred solution of alcohol **2.76** (2.1 g, 9.58 mmol) and BAIB (3.4 g, 10.54 mmol) in DCM (20 mL) at room temperature under nitrogen. The reaction mixture was stirred for 24 h and then diluted with DCM (10 mL) and quenched with an aq. sat. solution of $Na_2S_2O_3$. The aqueous layer was extracted with DCM (3 × 30 mL) and the combined organic layers washed with a saturated aqueous $NaHCO_3$ solution (80 mL), dried over MgSO4, concentrated under reduced pressure and purified by flash column chromatography (petroleum ether/ethyl acetate 4:1) affording aldehyde **2.78** (1.7 g, 84%) as a thick colourless oil.

R_f 0.47 (ethyl acetate/petroleum ether 4:1); $[\alpha]_D^{20}$ = -68.8 (c 5.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.48 (s, 9H, CH_3), 1.98-2.06 (m, 1H, H3), 2.18-2.28 (m, 1H, H3'), 2.48-2.53 (m, 2H, H4/H4'), 4.56 (ddd, 1H, *J* 2.0, 4.8 and 9.4 Hz, H2), 9.57 (d, 1H, *J* 2.0 Hz, CHO); δ_C (100 MHz, $CDCl_3$): 18.3 (CH_2, C3), 27.9 (CH_3), 31.2 (CH_2, C4), 64.2 (CH, C2), 84.2 (C), 149.4 (C=O), 173.1 (C=O), 197.0 (CHO). Data in agreement with literature.[199]

***(S)-tert-butyl 2-((R)-1-hydroxyprop-2-yn-1-yl)-5-oxopyrrolidine-1-carboxylate and (S)-tert-butyl 2-((S)-1-hydroxyprop-2-yn-1-yl)-5-oxopyrrolidine-1-carboxylate* 2.80a/b**



Ethynyl magnesium bromide **2.79** (1.8 mL of a 0.5 M solution in THF, 8.89 mmol) was added to a stirred solution of aldehyde **2.78** (94 mg, 0.44 mmol) in THF (2.0 mL) at 0 ºC under nitrogen. After 1 h the reaction mixture was quenched with an aq. sat. solution of NH_4Cl (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate/petroleum ether 1:1) affording alcohols **2.80a** and **2.80b** as two separable isomers (17 mg, 16% and 28 mg, 26%) as colourless oils.

***Less polar isomer:* 280a**

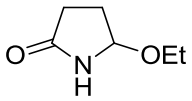
R_f 0.53 (ethyl acetate/petroleum ether 1:1); $[\alpha]_D^{20}$ = +63.8 (c 2.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.55 (s, 9H, CH_3), 2.12-2.23 (m, 2H, H3/H3'), 2.36-2.44 (m, 1H, H4), 2.51 (d, 1H, *J* 2.2 Hz, C≡CH), 2.77 (dt, 1H, *J* 10.0 and 17.8 Hz, H4'), 3.16 (d, 1H, *J* 6.0 Hz, OH), 4.28-4.32 (m, 1H, H2), 4.77-4.80 (m, 1H, C*H*OH); δ_C (100 MHz, $CDCl_3$): 19.5 (CH_2, C3), 28.0 (CH_3), 32.1 (CH_2, C4), 62.0 (CH, C2), 64.6 (CH, CHOH), 75.0 (C, C≡C), 81.3 (CH, C≡CH), 83.9 (C), 151.2 (C=O), 174.6 (C=O); ν_{max}/cm^{-1} (neat) 3449, 3259, 2977, 2920, 2112, 1763 (C=O), 1370,

1291, 1252, 1151; m/z (ES+) 501 (100%), 262 ([M+Na]$^+$, 50%), 140 ([(M-Boc)+H]$^+$, 50%); HRMS calc. for $C_{12}H_{18}O_4N$ 240.1230, found 240.1227 [M+H]$^+$.

***More polar isomer:* 280b**

R_f 0.41 (ethyl acetate/petroleum ether 1:1); $[\alpha]_D^{20}$ = -97.0 (c 2.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.54 (s, 9H, CH_3), 2.11-2.20 (m, 1H, H3), 2.22-2.30 (m, 1H, H3'), 2.41-2.49 (m, 2H, H4), 2.47 (d, 1H, *J* 2.2 Hz, C≡CH), 2.56 (d, 1H, *J* 4.1 Hz, OH), 2.80 (dt, 1H, J 10.2 and 18.0 Hz, H4'), 4.32 (ddd, 1H, *J* 1.9, 5.5 and 8.7 Hz, H2), 4.79 (brs, 1H, CHOH); δ_C (100 MHz, $CDCl_3$): 18.9 (CH_2, C3), 28.0 (CH_3), 31.8 (CH_2, C4), 60.7 (CH, C2), 63.4 (CH, C*H*OH), 75.3 (C, C≡C), 81.5 (CH, C≡CH), 83.8 (C), 150.7 (C=O), 174.2 (C=O); ν_{max}/cm^{-1} (neat) 3447, 3253, 2978, 2918, 2110, 1761 (C=O), 1370, 1293, 1254, 1153; m/z (ES+) 501 (100%), 262 ([M+Na]$^+$, 20%), 140 ([(M-Boc)+H]$^+$, 10%); HRMS calc. for $C_{12}H_{17}O_4NNa$ 262.1050, found 262.1050 [M+Na]$^+$.

5-Ethoxypyrrolidin-2-one 2.90

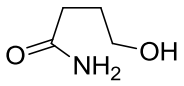


$NaBH_4$ (2.9 g, 75.7 mmol) was added over 2 h to a stirred solution of succinimide **2.88** (5.0 g, 50.5 mmol) in ethanol (225 mL) at 0 ºC. Every 15 min for 5 h, 4 drops of HCl (2 M in ethanol) was added over 5 h. After 5 h, the pH was adjusted to 4 and the slurry was stirred for 2 h. The reaction mixture was neutralised with KOH (3% in ethanol). Evaporation of the solvents under vacuum afforded a white solid which was triturated with diethyl ether. The resulting suspension was filtered and the filtrate concentrated under vacuum and purified by flash column chromatography on deactivated (10% w/W H_20) alumina (Et_2O), affording ethoxy lactam **2.90** (2.5 g, 41%) as a white solid and 4-hydroxybutanamide **2.89** (624 mg, 12%) as white solid.

R_f 0.46 (MeOH/DCM 1:9); mp = 56-60 ºC [lit.[127] 56-58 ºC]; δ_H (400 MHz, $CDCl_3$): 1.22 (t, 3H, *J* 7.0 Hz, CH_3), 1.96-2.14 (m, 1H, H4), 2.15-2.39 (m, 2H, H3/H4'), 2.49-2.58 (m, 1H, H3), 3.38-3.47 (m, 1H, OC*H*H'), 3.54-3.61 (m, 1H, OCH*H*'), 4.98 (d, 1H, *J* 6.0 Hz, H5), 7.86 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$): 15.2

(CH_3), 28.3 (CH_2), 28.4 (CH_2), 62.8 (CH_2, OCH_2), 85.8 (CH, C5), 179.5 (C=O). Data in agreement with literature.[127]

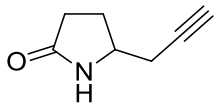
4-Hydroxybutanamide 2.89



2.91

R_f 0.13 (MeOH/DCM 1:9). mp = 51-54 ºC [lit.[200] 52-53 ºC]; δ_H (400 MHz, DMSO-d_6): 1.06 (p, 2H, *J* 6.9 Hz, H3), 1.52 (q, 2H, *J* 6.9 Hz, H2), 2.82 (t, 2H, *J* 6.9 Hz, H4), 6.13 (s, 1H, NH), 6.68 (s, 1H, NH); δ_C (100 MHz, DMSO-d_6): 28.4 (CH_2, C3), 31.8 (CH_2, C2), 60.3 (CH_2, C4), 174.36 (C=O). NMR in agreement with literature.[200]

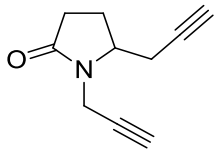
5-(Prop-2-yn-1-yl)pyrrolidin-2-one 2.61



From succinimide

Allenyltin **2.91** (360 μL of a 80% solution in toluene, 0.97 mmol) was added to a stirred solution of ethoxy lactam **2.90** (50 mg, 0.39 mmol) in anhydrous DCM (1 mL) at -30 ºC under argon. $BF_3{\cdot}OEt_2$ (96 μL, 110 mg, 0.77 mmol) was then added dropwise and the reaction was stirred for 7 h at -30 ºC. The reaction mixture was quenched with an aq. sat. solution of $NaHCO_3$ (2 mL) and stirred vigorously for 2 minutes. The layers were separated, the aqueous phase was extracted with DCM (3 × 3 mL) and the combined organic layers were dried over $MgSO_4$, concentrated under vacuum, and purified by flash column chromatography (ethyl acetate/petroleum ether 1:1 to 1:0) to afford allene **2.65** (0.9 mg, 2%) as a colourless oil, a mixture of alkyne **2.61** and allene **2.65** (9:1, 13.8 mg) and alkyne **2.61** (22.2 mg, 47%) as a yellow powder. The overall yield of alkyne **2.61** was 73% (35 mg). Data for the compounds was in accordance with those previously described.

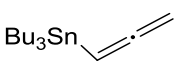
***1,5-Di(prop-2-yn-1-yl)pyrrolidin-2-one* 1.132**



NaH (12 mg of a 60% suspension in mineral oil, 0.51 mmol) was added to a stirred solution of alkyne **2.61** (48 mg, 0.390 mmol) in anhydrous DMF (1.0 mL) at 0 ºC under nitrogen. After 30 minutes, propargyl bromide **2.9** (91 μL of a 80% solution in toluene, 0.82 mmol) was added and the reaction mixture was warmed to rt and stirred for 45 min. The reaction mixture was quenched with water (3 mL) and extracted with ethyl acetate (3 × 3 mL) and the combined organic layers dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (ethyl acetate/petroleum ether 7:3) to afford dialkyne **1.132** (52 mg, 83%) as a yellowish oil.

R_f: 0.46 (petroleum ether/ethyl acetate 1:1); δ_H (400 MHz, $CDCl_3$): 1.88-2.00 (m, 1H, H4), 1.97 (t, 1H, *J* 2.6 Hz, C≡CH), 2.20 (t, 1H, *J* 2.3 Hz, C≡CH), 2.16-2.26 (m, 2H, H4'), 2.27-2.38 (m, 1H, H3), 2.44-2.53 (m, 3H, H3'/CCHH'), 3.67 (dd, 1H, *J* 2.3 and 17.8 Hz, NC*H*H'), 3.92 (dq, 1H, *J* 5.0 and 9.8 Hz, H5), 4.55 (dd, 1H, *J* 2.3 and 17.8 Hz, NCH*H*'); δ_C (100 MHz, $CDCl_3$): 23.1 (CH_2), 23.3 (CH_2), 29.9 (CH_2), 30.0 (CH_2), 55.3 (CH, C5), 71.3 (C, C≡C), 72.4 (C, C≡C), 77.5 (CH, C≡CH), 78.9 (CH, C≡CH), 174.6 (C=O); ν_{max}/cm^{-1} (neat) 3284, 2960, 2919, 2118, 1676 (C=O), 1416, 1250, 1180; m/z (ES+) 162 ($[M+H]^+$, 100%); HRMS calc. for $C_{10}H_{12}ON$ 162.0913, found 162.0917 $[M+H]^+$.

Tributyl(propa-1,2-dien-1-yl)stannane 2.91

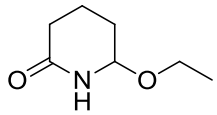


Tributyltin chloride (5.4 mL, 6.5 g, 20.00 mmol) was added to a stirred solution of magnesium (631 mg, 26.00 mmol) and lead bromide (366 mg, 1.00 mmol) in THF (20 mL) at room temperature under argon. Propargyl bromide **2.9** (2.8 mL of an 80% solution in toluene, 26.00 mmol) was added dropwise and the reaction was slightly heated with a heat gun, then stirred for 2.5 h at room temperature. The reaction mixture was quenched with an aq. sat. solution of

NH_4Cl (20 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 40 mL) and the combined organic layers washed with brine (40 mL), dried over Na_2SO_4, concentrated under vacuum and purified by flash column chromatography on deactivated (10% w/w H_2O) alumina (hexane) affording allenyl tin **2.91** (21.2 g, 81%) as a colourless liquid.

R_f 0.5 (hexane); δ_H (400 MHz, $CDCl_3$): 0.90 (t, 9H, *J* 7.3 Hz, CH_3), 0.95-0.99 (m, 6H, CH_2), 1.27-1.36 (m, 6H, CH_2), 1.43-1.57 (m, 6H, CH_2), 4.14 (d, 2H, *J* 7.1 Hz, CH_2), 4.97 (t, 1H, *J* 7.1 Hz, CH); δ_C (100 MHz, $CDCl_3$): 10.3 (CH_2), 13.7 (CH_3), 27.2 (CH_2), 28.9 (CH_2), 63.1 (CH_2), 73.9 (CH), 209.8 (C). NMR in agreement with literature.[130]

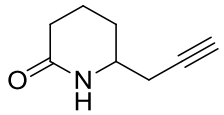
6-Ethoxypiperidin-2-one 2.105



Sodium borohydride (3.55 g, 94.30 mmol) was added portionwise to a stirred solution of piperidine-2,6-dione **2.104** (4.76 g, 42.10 mmol) in ethanol (250 mL) at 0 °C. Every 15 min for 5 h, 4 drops of HCl (2 M in ethanol) were added. After 5 h, the reaction mixture was acidified (pH 3) by the addition of HCl (2 M in ethanol) and stirred for an additional 2 h at 0 °C. The reaction was neutralized with KOH (3% in ethanol) and the resulting milky solution concentrated under vacuum. The resultant white solid was extracted with DCM (3 x 100 mL), the organic layer filtered, and the filtrate was concentrated under vacuum and purified by flash column chromatography (5% MeOH/DCM) to yield 6-ethoxypiperidin-2-one **2.105** (3.0 g, 50%) as a white solid.

R_f 0.37 (5% MeOH/DCM); mp = 112-115 ºC [lit.[201] 122- 123 ºC]; δ_H (400 MHz, $CDCl_3$): 1.21 (t, 3H, *J* 7.0 Hz, CH_3), 1.65-1.76 (m, 1H, H4), 1.77-1.82 (m, 1H, H5), 1.88-1.96 (m, 1H, H5'), 2.02-2.07 (m, 1H, H4'), 2.26-2.37 (m, 1H, H3), 2.38-2.46 (m, 1H, H3'), 3.42 (dq, 1H, *J* 8.9 and 7.0 Hz, OC*H*H'), 3.62 (dq, 1H, *J* 8.9 and 7.0 Hz, OCH*H*'), 4.66 (app q, 1H, *J* 3.5 Hz, H6), 6.93 (s, 1H, NH); δ_C (100 MHz, $CDCl_3$): 15.3 (CH_3), 16.2 (CH_2, C4), 27.9 (CH_2, C5), 31.7 (CH_2, C3), 62.7 (OCH_2), 81.8 (CH, C6), 172.8 (C=O). Data in agreement with literature.[201]

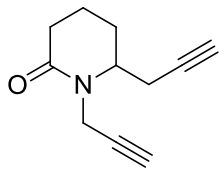
6-(Prop-2-yn-1-yl)piperidin-2-one 2.106



To a stirred solution of 6-ethoxylactam **2.105** (500 mg, 3.49 mmol) in DCM (5.0 mL) at -40 °C under argon was added allenyl tin **2.91** (2.6 mL, 2.87 g, 8.73 mmol). $BF_3.OEt_2$ (862 μL, 991 mg, 6.98 mmol) was then added dropwise and the reaction was stirred at -40 ºC for 7 h. The reaction mixture was then quenched with an aq. sat. solution of $NaHCO_3$ (30 mL), extracted with ethyl acetate (3 × 30 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography (petroleum ether/ethyl acetate 7:3 to 0:1) affording alkyne **2.106** contaminated with the correspondening allene. The mixture was crystallised from ethyl acetate to yield alkyne **2.106** (275 mg, 55%) as a pale yellow solid.

R_f 0.37 (5% MeOH/DCM); mp = 87-89 ºC [lit.[128] 98-100 ºC]; δ_H (400 MHz, $CDCl_3$): 1.41-1.50 (m 1H, H5), 1.65-1.76 (m, 1H, H4), 1.86-1.94 (m, 1H, H4'), 1.94-2.01 (m, 1H, H5'), 2.08 (t, 1H, *J* 2.6 Hz, C≡CH), 2.24-2.33 (m, 2H, H3/C*H*H'), 2.36-2.43 (m, 2H, H3'/CH*H*'), 3.54 (tt, 1H, *J* 4.8 and J 9.2 Hz, H6), 6.20 (brs, 1H, NH); δ_C (100 MHz, $CDCl_3$): 19.5 (CH_2, C4), 26.7 (CH_2, CHH), 28.1 (CH_2, C5), 31.3 (CH_2, C3), 51.8 (CH, C6), 71.6 (C, C≡C), 79.6 (CH, C≡CH), 172.1 (C=O). Data in agreement with literature.[128]

***1,6-Di(prop-2-yn-1-yl)piperidin-2-one* 1.133**

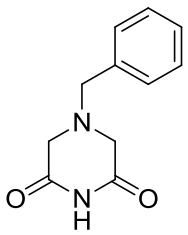


NaH (191 mg of a 60% suspension in mineral oil, 4.78 mmol) was added to a stirred solution of alkyne **2.106** (437 mg, 3.19 mmol) in DMF (8 mL) at 0 °C under argon and the reaction mixture stirred for 30 minutes. Propargyl bromide **2.9** (745 μL of an 80% solution in toluene, 6.69 mmol) was added dropwise and the reaction mixture was stirred for an additional 30 minutes at 0 ºC. The reaction was quenched with aq. sat. solution of NH_4Cl (10 mL), extracted with

ethyl acetate (3 × 10 mL), dried over $MgSO_4$, concentrated under vacuum and purified by flash chromatography (petroleum ether /ethyl acetate 1:1) to afford dialkyne **1.133** (293 mg, 90%) as a pale white solid.

R_f 0.30 (ethyl acetate/petroleum ether 1:1); mp = 66-68 ºC; δ_H (400 MHz, $CDCl_3$): 1.69-1.79 (m, 1H, H4), 1.84-1.96 (m, 2H, H5/H4'), 2.03-2.10 (m, 1H, H5'), 2.04 (t, 1H, *J* 2.7 Hz, C≡CH), 2.22 (t, 1H, *J* 2.5 Hz, C≡CH), 2.41 (app t, 2H, *J* 6.6 Hz, H3/H3'), 2.52 (ddd, 1H, *J* 2.9, 8.5 and 16.9 Hz, CC*H*H'), 2.63 (dt, 1H, J 2.9 and 16.9 Hz, CCH*H*'), 3.82-3.87 (m, 1H, H6), 3.84 (dd, *J* 2.5 and 17.6 Hz, NC*H*H'), 4.77 (dd, *J* 2.5 and 17.6 Hz, NCH*H*'); δ_C (100 MHz, $CDCl_3$): 17.5 (CH_2, C4), 23.1 (CH_2, CHH), 27.0 (CH_2, C5), 32.2 (CH_2, C3), 33.6 (CH_2, NCHH), 54.7 (CH, C6), 71.4 (C, C≡C), 72.1 (C, C≡C), 78.7 (CH, C≡CH), 79.9 (CH, C≡CH), 170.1 (C=O); ν_{max}/cm^{-1} (neat) 3280, 2965, 2923, 2116, 1672 (C=O), 1418, 1251, 1181; m/z (AP+) 176 ($[M+H]^+$, 100%); HMRS calc. for $C_{11}H_{14}ON$ 176.1070, found 176.1072 $[M+H]^+$.

4-Benzylpiperazine-2,6-dione 2.108

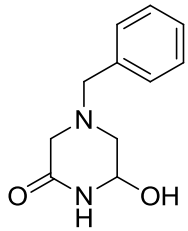


To a stirred solution of 2,2'-(benzylazanediyl)diacetic acid **2.107** (2.5 g, 11.2 mmol) in DMF (35 mL) under argon was added ammonium formate (2.1 g, 33.6 mmol). The reaction was heated under reflux for 22 h, then diluted with ethyl acetate (50 mL) and washed with saturated aqueous $NaHCO_3$ solution (50 mL). The organic phase was washed with brine (3 × 50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the 4-benzylpiperazine-2,6-dione **2.118** (3.0 g, 65%) as a white solid.

R_f 0.32 (ethyl acetate/petroleum ether 3:7); mp = 103-105 ºC [lit.[202] 105-106 ºC]; δ_H (400 MHz, $CDCl_3$): 3.36 (s, 4H, H3/H5), 3.66 (s, 2H, CH_2), 7.27-7.37 (m, 5H, HAr), 9.11 (s, 1H, NH); δ_C (100 MHz, $CDCl_3$): 55.2 (CH_2, C3), 55.2 (CH_2,

C5) 60.5 (CH_2, CH_2Ph), 128.1 (CHAr), 128.7 (CHAr), 129.1 (CHAr), 135.4 (CAr), 170.7 (C=O). Data in agreement with literature.[202]

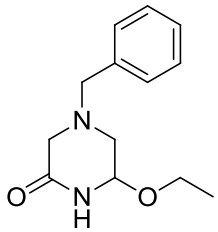
***4-Benzyl-6-hydroxypiperazin-2-one* 2.109**



Sodium borohydride (1.2 g, 32.70 mmol) was added portionwise over 2 h to a stirred solution of 4-benzylpiperazine-2,6-dione **2.108** (3.0 g, 14.6 mmol) in ethanol (87 mL) at 0 °C. Every 15 minutes for 5 h, 2 drops of HCl (2 M in ethanol) were added, keeping the temperature at 0 °C. The reaction was acidified (pH ~3) by addition of HCl (2 M in ethanol) and stirred for an additional 2 h at 0 °C. The reaction was neutralized with KOH (3% in ethanol) and the resulting milky solution concentrated under vacuum. The resultant white solid was extracted with DCM (3 × 100 mL), the organic layer filtered then the filtrate was concentrated under vacuum and purified by flash column chromatography (5% MeOH/DCM) to yield alcohol **2.109** (1.9 g, 62%) as a white solid.

R_f 0.33 (1:19 MeOH/DCM); mp = 114-116 ºC; δ_H (400 MHz, $CDCl_3$): 2.49 (dd, 1H, *J* 2.2 and 11.7 Hz, H5), 2.77 (brd, 1H, *J* 11.7 Hz, H5'), 2.86 (d, 1H, *J* 16.7 Hz, H3), 3.30 (d, 1H, *J* 16.7 Hz, H3'), 3.50 (d, 1H, *J* 12.9 Hz, C*H*H'Ph), 3.55 (d, 1H, *J* 12.9 Hz, CH*H*'Ph), 4.02 (d, 1H, *J* 9.8 Hz, OH), 4.78 (brs, 1H, H6), 7.19-7.28 (m, 5H, HAr); δ_C (100 MHz, $CDCl_3$): 55.5 (CH_2, C5), 57.0 (CH_2, C3), 61.4 (CH_2, CH_2Ph), 74.2 (CH, C6), 127.8 (CHAr), 128.6 (CHAr), 129.1 (CHAr), 136.1 (CAr), 169.7 (C=O); ν_{max}/cm^{-1} (neat) 3190, 3000, 2841, 2818, 1665 (C=O), 1452, 1319, 1087; m/z (AP+) 207 ($[M+H]^+$, 100%); HMRS calc. for $C_{11}H_{15}O_2N_2$ 207.1128, found 207.1128 $[M+H]^+$.

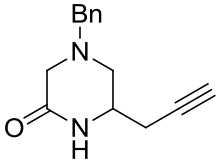
***4-Benzyl-6-ethoxypiperazin-2-one* 2.110**



PTSA (341 mg, 1.79 mmol) was added to a stirred solution of alcohol **2.109** (1.9 g, 8.96 mmol) in ethanol (30 mL) and the reaction mixture heated at 60 °C for 4 h. The reaction was quenched with an aq. sat. solution of $NaHCO_3$ (30 mL). The reaction mixture was extracted with DCM (3 × 30 mL) and the combined organic layers dried over $MgSO_4$ and concentrated under vacuum to yield compound **2.110** (quantitative) as a white solid which was used in the next step without further purification.

R_f 0.35 (EA); mp = 89-90 ºC; δ_H (400 MHz, $CDCl_3$): 1.21 (t, 3H, *J* 7.0 Hz, CH_3), 2.67 (dd, 1H, *J* 3.8 and 12.2 Hz, H5), 2.73 (dd, 1H, *J* 4.2 and 12.2 Hz, H5'), 3.07 (d, 1H, *J* 16.6 Hz, H3), 3.26 (d, 1H, *J* 16.6 Hz, H3'), 3.43 (dq, 1H, *J* 7.0 and 9.0 Hz, OC*H*H'), 3.56-3.68 (m, 1H, OCH*H*'), 3.57 (d, 1H, *J* 13.1 Hz, C*H*H'Ph), 3.66 (d, 1H, *J* 13.1 Hz, CH*H*'Ph), 4.68-4.70 (m, 1H, H6), 6.71 (brs, 1H, NH), 7.28-7.35 (m, 5H, HAr); δ_C (100 MHz, $CDCl_3$): 15.3 (CH_3), 53.2 (CH_2, C5), 56.7 (CH_2, C3), 61.4 (CH_2, CH_2Ph), 63.1 (CH_2, OCH_2), 80.9 (CH, C6), 127.6 (CHAr), 128.5 (CHAr), 129.1 (CHAr), 136.4 (CAr), 169.7 (C=O); ν_{max}/cm^{-1} (neat) 3198, 3065, 2972, 2899, 1675 (C=O), 1496, 1420, 1336, 1311, 1282, 1081; m/z (AP+) 235 ($[M+H]^+$, 100%); HMRS calc. for $C_{13}H_{19}O_2N_2$ 235.1441, found 235.1439 $[M+H]^+$.

***4-Benzyl-6-(prop-2-yn-1-yl)piperazin-2-one* 2.8**

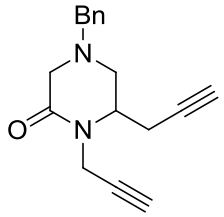


Allenyl tin **2.91** (190 μL, 168 mg, 0.51 mmol) was added to a stirred solution of ethoxy lactam **2.110** (48 mg, 0.20 mmol) in DCM (1.0 mL) at -40 ºC under argon. $BF_3{\cdot}OEt_2$ (50 μL, 58 mg, 0.41 mmol) was added dropwise and the reaction mixture heated under reflux for 6 h. The reaction was then quenched with an

aq. sat. solution of $NaHCO_3$ solution (5 mL), extracted with ethyl acetate (3 × 5 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography (petroleum ether/ethyl acetate 7:3 to 0:1) affording alkyne **2.8** contaminated with the corresponding allene which was recrystallised from ethyl acetate to yield alkyne **2.8** (25 mg, 54%) as a white solid.

R_f 0.47 (EA); mp = 169-171 ºC; δ_H (400 MHz, $CDCl_3$): 2.07 (t, 1H, *J* 2.6 Hz, C≡CH), 2.42-2.48 (m, 3H, H5, CHH'), 2.79 (dd, 1H, *J* 4.2 and 11.8 Hz, H5'), 3.14 (d, 1H, *J* 16.7 Hz, H3), 3.21 (d, 1H, *J* 16.7 Hz, H3'), 3.60 (s, 2H, CH_2Ph), 3.61-3.67 (m, 1H, H6), 6.11 (brs, 1H, NH), 7.27-7.35 (m, 5H, HAr); δ_C (100 MHz, $CDCl_3$): 24.7 (CH_2), 50.6 (CH, C6), 53.1 (CH_2, C5), 56.9 (CH_2, C3), 61.5 (CH_2, CH_2Ph), 71.5 (C, C≡C), 79.6 (CH, C≡CH), 127.6 (CHAr), 128.5 (CHAr), 128.9 (CHAr), 136.8 (CAr), 169.2 (C=O); ν_{max}/cm^{-1} (neat) 3227, 3064, 2925, 2803, 2762, 2000, 1658 (C=O), 1421, 1345; m/z (AP+) 229 ($[M+H]^+$, 100%); HMRS calc. for $C_{14}H_{17}N_2O$ 229.1335, found 229.1337 $[M+H]^+$.

4-Benzyl-1,6-di(prop-2-yn-1-yl)piperazin-2-one 1.128



NaH (24 mg of a 60% suspension in mineral oil, 0.61 mmol) was added to a stirred solution of alkyne **2.8** (100 mg, 0.44 mmol) in DMF (1.0 mL) at 0 °C under argon. After 30 minutes propargyl bromide **2.9** (102 μL of an 80% solution in toluene, 0.92 mmol) was added dropwise and the reaction mixture was stirred for an additional 30 minutes at 0 ºC. The reaction was quenched with an aq. sat. solution of NH_4Cl (5 mL), extracted with ethyl acetate (3 × 5 mL) and the combined organic layers dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (petroleum ether /ethyl acetate 1:1) to afford dialkyne **1.128** (110 mg, 93%) as a pale yellow oil.

R_f 0.36 (petroleum ether/ethyl acetate 7:3); δ_H (400 MHz, $CDCl_3$): 1.85 (t, 1H, *J* 2.8 Hz, C≡CH), 2.15 (t, 1H, *J* 2.5 Hz, C≡CH), 2.45 (dd, 1H, *J* 3.4 and 11.9, H5),

2.51 (dt, 1H, *J* 16.6 and 2.8 Hz, CC*H*H'), 2.68 (ddd, 2.8, 9.3 and 16.6 Hz, CCH*H*'), 2.86 (d, 1H, *J* 16.6 Hz, H3), 2.96 (ddd, 1H, *J* 1.2, 3.4 and 11.9 Hz, H5'), 3.27 (dd, 1H, *J* 1.2 and 16.6 Hz, H3'), 3.43 (d, 1H,*J* 13.0 Hz, C*H*H'Ph), 3.47 (d, 1H, *J* 13.0 Hz, CH*H*'Ph), 3.61-3.66 (m, 1H, H6), 3.77 (dd, 1H, *J* 2.5 and 17.6 Hz, NC*H*H'), 4.58 (dd, 1H, *J* 2.5 and 17.6 Hz, NCH*H*'), 7.13-7.24 (m, 5H, HAr); δ_C (100 MHz, $CDCl_3$): 21.8 (CH_2), 33.6 (CH_2), 52.3 (CH_2, C5), 54.9 (CH, C6), 57.3 (CH_2, C3), 61.5 (CH_2, CH_2Ph), 71.0 (C, C≡C), 72.6 (C, C≡C), 78.2 (CH, C≡CH), 80.3 (CH, C≡CH), 127.5 (CHAr), 128.4 (CHAr), 129.0 (CHAr), 136.8 (CAr), 167.1 (C=O); ν_{max}/cm^{-1} (neat) 3290, 2962, 2921, 2115, 1679 (C=O), 1417, 1251, 1183; m/z (AP+) 267 ($[M+H]^+$, 100%); HMRS calc. for $C_{17}H_{18}ON_2$ 267.1492, found 267.1496 $[M+H]^+$.

General procedure for the transition-metal catalysed [2+2+2] cyclotrimerisation reactions:

Diethylacetylene dicarboxylate **2.112a** (355 μL, 377 mg, 2.26 mmol) was added to a stirred solution of dialkyne **1.132** (73 mg, 0.45 mmol), Cp*RuCodCl (17 mg, 0.045 mmol) in anhydrous degassed (three cycles of freeze-pump-thaw) toluene (2.0 mL) under argon. The mixture was heated to reflux for 2.5 h then the solvent removed under vacuum. Purification of the residue by flash column chromatography (petroleum ether/ethyl acetate 9:1 to 0:1) yielded the tricyclic adduct **2.116a** (104 mg, 70%) as a brown oil, hexaethyl benzene-1,2,3,4,5,6-hexacarboxylate **2.113a** (276 mg, 44%) as a pale yellow solid and 1,5-Di(benzyl-1,2,3,4-tetracarboxylic acid tetraethyl ester)-pyrrolidin-2-one **2.215a** (61 mg, 16%) as a dark orange oil.

The percentage yield and the appearance of the compounds obtained in these cyclotrimerisation reactions are listed below.

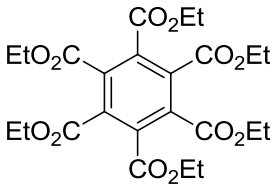
Compound No	% yield	mass (mg)	appearence
2.114a	21	32	Brown orange oil
2.113b	22	239	Orange oil
2.115b	17	61	Orange oil
2.116b	34	52	Yellow oil

2.113g	32	426	White solid
2.116g	1	2	Colourless oil
2.117a	46	73	Dark brown oil
2.118a	8	31	dark brown oil
2.117b	28	39	Red oil
2.118b	8	27	Dark orange oil
2.117g	5	8	Yellow oil
2.119a	39	56	Yellow oil
2.120a	4	12	Yellow oil

Table XXXVI – Yield and appearance of compounds obtained through the [2+2+2] cyclotrimerisation of alkynes.

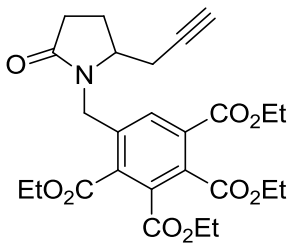
The ^{13}C NMR spectrum of some cyclic products often show superimposition of the CH_3 and OCH_2 carbons, nevertheless it can be confidently stated that it is the right compound; all other characterisation matches the desired structure.

Hexaethyl benzene-1,2,3,4,5,6-hexacarboxylate 2.113a



R_f 0.33 (petroleum ether/ethyl acetate 7:3); mp = 64-67 ºC [lit.[203] 74 ºC]; δ_H (400 MHz, $CDCl_3$): 1.28 (t, 18 H, *J* 7.2 Hz, CH_3), 4.25 (q, 12H, *J* 7.2 Hz, OCH_2); δ_C (100 MHz, $CDCl_3$): 13.8 (CH_3), 62.6 (CH_2), 133.8 (C), 164.8 (CO). Data in agreement with literature.[203]

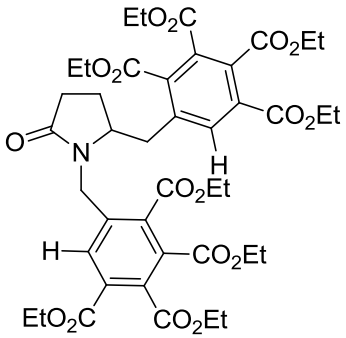
***Tetraethyl 5-((2-oxo-5-(prop-2-yn-1-yl)pyrrolidin-1-yl)methyl)benzene-1,2,3,4-tetracarboxylate* 2.114a**



R_f 0.42 (ethyl acetate/petroleum ether 7:3); δ_H (400 MHz, $CDCl_3$): 1.31-1.37 (m, 12H, CH_3), 1.93-2.01 (m, 1H, H4), 1.97 (t, 1H, *J* 2.6 Hz, C≡CH), 2.13-2.23 (m,

1H, H4'), 2.32-2.45 (m, 3H, H3, CHH'), 2.57-2.66 (m, 1H, H3'), 3.53-3.58 (m, 1H, H5), 4.17 (d, 1H, *J* 15.8 Hz, NCHH), 4.15-4.39 (m, 8H, OCH_2), 5.10 (d, 1H, *J* 15.8 Hz, NCHH'), 7.96 (s, 1H, HAr); δ_C (100 MHz, $CDCl_3$): 13.9 (CH_3), 13.9 (CH_3), 14.1 (CH_3), 23.1 (CH_2, C4), 23.4 (CH_2), 29.8 (CH_2, C3), 41.3 (CH_2), 55.4 (CH, C5), 62.1 (CH_2, OCH_2), 62.2 (CH_2, OCH_2), 62.5 (CH_2, OCH_2), 62.6 (CH_2, OCH_2), 71.5 (C, C≡C), 79.0 (CH, C≡CH), 130.8 (CAr), 131.2 (CAr), 132.7 (CHAr), 134.4 (CAr), 136.2 (CAr), 136.4 (CAr), 164.6 (C=O), 165.3 (C=O), 166.5 (C=O), 166.6 (C=O), 175.5 (C=O); ν_{max}/cm^{-1} (neat) 3309, 3059, 2985, 1727 (C=O), 1690 (C=O), 1420, 1368, 1266, 1244; m/z (AP+) 502 ($[M+H]^+$, 100%); HMRS calc. for $C_{26}H_{32}NO_9$ 502.2072, found 502.2068 $[M+H]^+$.

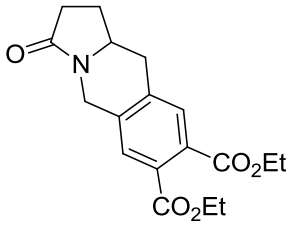
***1,5-Di(benzyl-1,2,3,4-tetracarboxylic acid tetraethyl ester)-pyrrolidin-2-one* 2.115a**



R_f 0.36 (ethyl acetate/petroleum ether 7:3) ; δ_H (400 MHz, $CDCl_3$): 1.24-1.31 (m, 24 H, CH_3), 1.69-1.86 (m, 2H, H4/H4'), 2.26-2.34 (m, 1H, H3), 2.41 (dd, 1H, *J* 8.7 and 17.3 Hz, H3'), 2.49 (dd, 1H, *J* 10.3 and 13.2 Hz, CC*H*H'), 3.15 (dd, 1H, *J* 3.9 and 13.2 Hz, CCH*H*'), 3.70 (m, 1H, H5), 4.25 (d, 1H, *J* 13.7 Hz, NC*H*H'), 4.21-4.31 (m, 16H, OCH_2), 5.00 (d, 1H, *J* 13.7 Hz, NCH*H*'), 7.82 (s, 1H, HAr), 7.88 (s, 1H, HAr); δ_C (100 MHz, $CDCl_3$): 13.8 (CH_3), 13.9 (CH_3), 14.0 (CH_3), 14.0 (CH_3), 23.1 (CH_2, C4), 29.2 (CH_2, C3), 35.8 (CH_2), 41.5 (CH_2), 58.1 (CH, C5), 62.1 (CH_2, OCH_2), 62.2 (CH_2, OCH_2), 62.4 (CH_2, OCH_2), 62.4 (CH_2, OCH_2), 62.5 (CH_2, OCH_2), 130.9 (CAr), 131.1 (CAr), 131.2 (CAr), 131.3 (CAr), 132.1 (CHAr), 133.7 (CAr), 133.8 (CHAr), 134.3 (CAr), 135.8 (CAr), 136.8 (CAr), 137.0 (CAr), 137.2 (CAr), 164.5 (C=O), 164.5 (C=O), 165.4 (C=O), 165.4 (C=O), 166.4 (C=O), 166.4 (C=O), 166.6 (C=O), 166.7 (C=O), 175.3 (C=O); ν_{max}/cm^{-1} (neat) 2983, 2940, 2908, 1722 (C=O), 1694 (C=O), 1445, 1415, 1233,

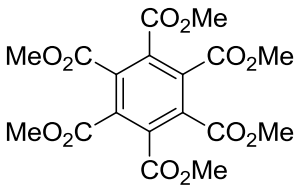
1196, 1177, 1156, 1101, 1018; m/z (AP+) 843 ($[M+2H]^+$, 50%), 842 ($[M+H]^+$, 100%); HMRS calc. for $C_{42}H_{55}N_2O_{17}$ 859.3495, found 859.3497 $[M+NH_4]^+$.

***Diethyl 3-oxo-1,2,3,5,10,10a-hexahydropyrrolo[1,2-b]isoquinoline-7,8-dicarboxylate* 2.116a**



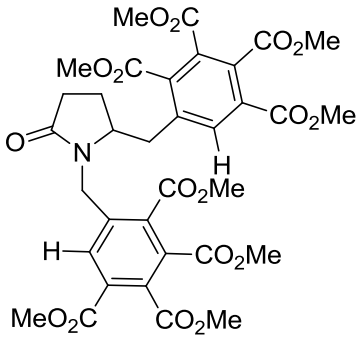
R_f 0.18 (ethyl acetate); δ_H (400 MHz, $CDCl_3$): 1.34 (t, 3H, *J* 7.1 Hz, CH_3), 1.34 (t, 3H, *J* 7.1 Hz, CH_3), 1.78-1.86 (m, 1H, H1), 2.37-2.49 (m, 3H, H1', H2, H2'), 2.70 (dd, 1H, *J* 11.4 and 15.7 Hz, H10), 3.02 (dd, 1H, *J* 3.7 and 15.7 Hz, H10'), 3.72-3.79 (m, 1H, H10a), 4.26 (d, 1H, *J* 18.2 Hz, H5), 4.33 (q, 2 H, *J* 7.1 Hz, OCH_2), 4.33 (q, 2 H, *J* 7.1 Hz, OCH_2), 4.97 (d, 1H, *J* 18.2 Hz, H5'), 7.47 (s, 1H, HAr), 7.49 (s, 1H, HAr); δ_C (100 MHz, $CDCl_3$): 14.1 (CH_3), 14.1 (CH_3), 25.1 (CH_2, C1), 29.9 (CH_2, C2), 36.6 (CH_2, C10), 42.3 (CH_2, C5), 53.4 (CH, C10a), 61.7 (CH_2, OCH_2), 61.7 (CH_2, OCH_2), 127.4 (CHAr), 129.8 (CHAr), 130.6 (CAr), 130.7 (CAr), 135.2 (CAr), 136.7 (CAr), 167.1 (C=O), 167.3 (C=O), 174.2 (C=O); ν_{max}/cm^{-1} (neat) 2982, 2940, 2908, 1718 (C=O), 1686 (C=O), 1442, 1419, 1285, 1255, 1180, 1129, 1018; m/z (AP+) 332 ($[M+H]^+$, 100%), 286 ($[M-OCH_2CH_3]^+$, 90%); HMRS calc. for $C_{18}H_{22}O_9N$ 332.1492, found 332.1496 $[M+H]^+$.

Hexamethyl benzene-1,2,3,4,5,6-hexacarboxylate 2.113b



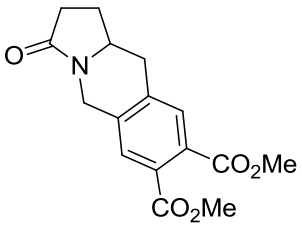
R_f 0.32 (ethyl acetate/petroleum ether 1:1); mp = 188-190 ºC [lit.[204] 186 ºC]; δ_H (400 MHz, $CDCl_3$): 3.82 (s, 18H); δ_C (100 MHz, $CDCl_3$): 52.9 (CH_3), 133.8 (C), 164.8 (CO). Data in agreement with literature.[204]

***1,5-Di(benzyl-1,2,3,4-tetracarboxylic acid tetramethyl ester)-pyrrolidin-2-one* 2.115b**



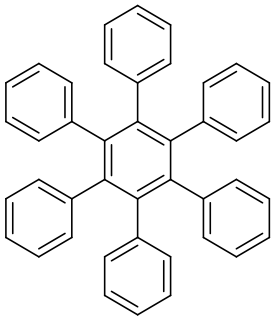
R_f 0.3 (ethyl acetate); δ_H (400 MHz, $CDCl_3$): 1.76 (m, 1H, H4), 1.88 (m, 1H, H4'), 2.34 (m, 1H, H3), 2.46 (dd, 1H, *J* 8.7 and 17.3 Hz, H3'), 2.54 (dd, 1H, *J* 9.9 and 13.4 Hz, C*H*H'), 3.15 (dd, 1H, *J* 4.3 and 13.4 Hz, CH*H*'), 3.69-3.75 (m, 1H, H5), 3.75 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 3.89 (s, 6H, CH_3), 4.18 (d, 1H, *J* 15.9 Hz, NC*H*H'), 5.02 (d, 1H, *J* 15.9 Hz, NCH*H*'), 7.88 (s, 1H, HAr), 7.92 (s, 1H, HAr); δ_C (100 MHz, $CDCl_3$): 23.3 (CH_2, C4), 29.1 (CH_2, C3), 36.1 (CH_2), 41.7 (CH_2), 53.0 (CH_3), 53.1 (CH_3), 53.1 (CH_3), 53.2 (CH_3), 58.0 (C5), 130.3 (CAr), 130.5 (CAr), 130.6 (CAr), 130.7 (CAr), 132.8 (CHAr), 134.0 (CAr), 134.2 (CHAr), 134.7 (CAr), 136.1 (CAr), 137.0 (CAr), 137.1 (CAr), 137.4 (CAr), 164.6 (C=O), 164.6 (C=O), 165.5 (C=O), 165.6 (C=O), 166.8 (C=O), 166.9 (C=O), 167.2 (C=O), 167.2 (C=O), 175.3 (C=O); ν_{max}/cm^{-1} (neat) 2950, 2850, 1723 (C=O), 1694 (C=O), 1420, 1375, 1237, 1175, 1017; m/z (AP+) 748 ($[M+NH_4]^+$, 100%), 731 ($[M+H]^+$, 10%); HMRS calc. for $C_{34}H_{39}N_2O_{17}$ 747.2243, found 747.2243 $[M+NH_4]^+$.

***Dimethyl 3-oxo-1,2,3,5,10,10a-hexahydropyrrolo[1,2-b]isoquinoline-7,8-dicarboxylate* 2.116b**



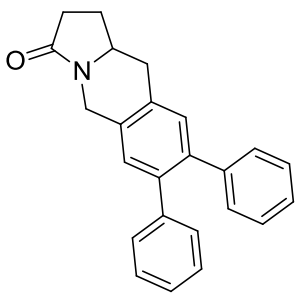
R_f 0.12 (ethyl acetate); δ_H (400 MHz, $CDCl_3$): 1.78-1.86 (m, 1H, H1), 2.37-2.49 (m, 3H, H1', H2, H2'), 2.70 (dd, 1H, *J* 11.2 and 15.6 Hz, H10), 3.01 (dd, 1H, *J* 3.7 and 15.6 Hz, H10'), 3.73-3.80 (m, 1H, H10a), 3.87 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 4.25 (d, 1H, *J* 18.3 Hz, H5), 4.97 (d, 1H, *J* 18.3 Hz, H5'), 7.47 (s, 1H, HAr), 7.49 (s, 1H, HAr); δ_C (100 MHz, $CDCl_3$): 25.1 (CH_2, C1), 29.9 (CH_2, C2), 36.6 (CH_2, C10), 42.3 (CH_2, C5), 52.7 (CH_3), 52.7 (CH_3), 53.4 (CH, C10a), 127.4 (CHAr), 129.8 (CHAr), 130.3 (CAr), 130.3 (CAr), 135.3 (CAr), 136.9 (CAr), 167.6 (C=O), 167.8 (C=O), 174.2 (C=O); ν_{max}/cm^{-1} (neat) 2954, 2845, 1719(C=O), 1675 (C=O), 1432, 1247, 1210, 1157, 1125; m/z (AP+) 304 ($[M+H]^+$, 100%); HMRS calc. for $C_{16}H_{16}O_5N$ 302.1023, found 302.1029 $[M-H]^+$.

3',4',5',6'-Tetraphenyl-1,1':2',1''-terphenyl 2.113g



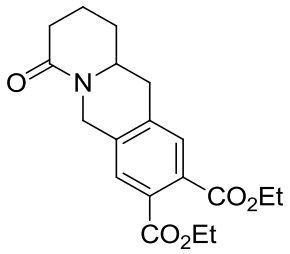
R_f 0.12 (ethyl acetate); mp = 458 ºC [lit.[205] 462 ºC]; δ_H (400 MHz, $CDCl_3$): 7.24-7.30 (m, 18H), 7.44-7.49 (m, 12H); δ_C (100 MHz, $CDCl_3$): 128.3, 128.4, 131.6. Data in agreement with literature.[205]

***7,8-Diphenyl-1,2,10,10a-tetrahydropyrrolo[1,2-b]isoquinolin-3(5H)-one* 2.116g**



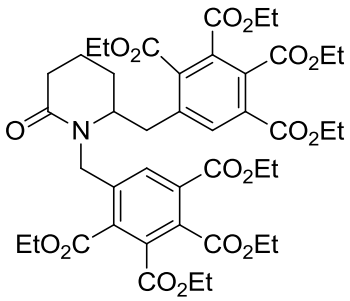
R_f 0.24 (ethyl acetate); δ_H (400 MHz, $CDCl_3$): 1.82-1.91 (m, 1H, H1), 2.40-2.54 (m, 3H, H1, H2, H2'), 2.79 (dd, 1H, *J* 11.3 and 15.3 Hz, H10), 3.05 (dd, 1H, *J* 3.7 and 15.3 Hz, H10'), 3.85-3.92 (m, 1H, H10a), 4.35 (d, 1H, *J* 17.6 Hz, H5), 5.04 (d, 1H, *J* 17.6 Hz, H5'), 7.10-7.13 (m, 4H, HAr), 7.19-7.23 (m, 8H, HAr); δ_C (100 MHz, $CDCl_3$): 25.4 (CH_2, C1), 30.2 (CH_2, C2), 36.6 (CH_2, C10), 42.4 (CH_2, C5), 54.1 (CH, C10a), 126.6 (CHAr), 126.6 (CHAr), 127.9 (CHAr), 128.0 (CHAr), 128.7 (CHAr), 129.8 (CHAr), 131.1 (CAr), 131.2 (CHAr), 132.5 (CAr), 139.1 (CAr), 139.4 (CAr), 140.8 (CAr), 140.9 (CAr), 174.3 (C=O); ν_{max}/cm^{-1} (neat) 2974, 2843, 1657 (C=O), 1444, 1335, 1264; m/z (AP+) 340 ($[M+H]^+$, 100%); HMRS calc. for $C_{24}H_{22}ON$ 340.1696, found 340.1699 $[M+H]^+$.

***Diethyl 4-oxo-2,3,4,6,11,11a-hexahydro-1H-pyrido[1,2-b]isoquinoline-8,9-dicarboxylate* 2.117a**



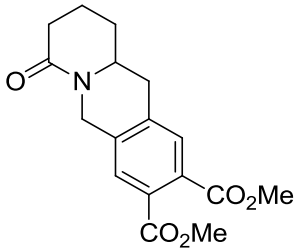
R_f 0.27 (ethyl acetate); δ_H (400 MHz, $CDCl_3$): 1.32 (t, 3H, *J* 7.2 Hz, CH_3), 1.38 (t, 3H, *J* 7.2 Hz, CH_3), 1.69-1.79 (m, 2H, H2, H1), 1.87-1.92 (m, 1H, H2'), 2.09-2.16 (m, 1H, H1'), 2.38-2.50 (m, 2H, H3/H3'), 2.79-2.91 (m, 2H, H11/H11'), 3.56-3.63 (m ,1H, H11a), 4.21 (d, 1H, *J* 18.3 Hz, H6), 4.32 (s, 2H, OCH_2), 4.32 (s, 2H, OCH_2), 5.34 (d, 1H, *J* 18.3 Hz, H6'), 7.44 (s, 1H, HAr), 7.48 (s, 1H, HAr); δ_C (100 MHz, $CDCl_3$): 14.1 (CH_3), 18.5 (CH_2, C2), 29.1 (CH_2, C1), 32.7 (CH_2, C3), 36.6 (CH_2, C11), 44.6 (CH_2, C6), 53.1 (CH, C11a), 61.6 (CH_2, OCH_2), 127.2 (CHAr), 128.9 (CHAr), 130.4 (CAr), 130.5 (CAr), 136.2 (CAr), 137.1 (CAr), 167.2 (C=O), 167.4 (C=O), 169.7 (C=O); ν_{max}/cm^{-1} (neat) 2982, 2940, 2904, 1718 (C=O), 1627 (C=O), 1444, 1367, 1296, 1274, 1244, 1129; m/z (AP+) 346 ($[M+H]^+$, 100%); HMRS calc. for $C_{19}H_{22}O_5N_1$ 344.1493, found 344.1497 $[M-H]^+$.

***1,6-Di(benzyl-1,2,3,4-tetracarboxylic acid tetraethyl ester)-piperidin-2-one* 2.118a**



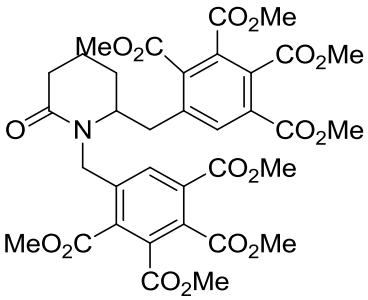
R_f 0.35 (ethyl acetate); δ_H (400 MHz, $CDCl_3$): 1.25-1.31 (m, 24H, CH_3), 1.53-1.61 (m, 2H, H5/H5'), 1.68-1.74 (m, 1H, H4), 1.91-1.97 (m, 1H, H4'), 2.42-2.50 (m, 2H, H3/H3'), 2.76 (dd, 1H, *J* 10.6 and 13.6 Hz, CC*H*H'), 3.20 (dd, 1H, *J* 4.0 and 13.6 Hz, CCH*H*'), 3.54-3.60 (m, 1H, H6), 4.20-4.31 (m, 17H, OCH_2/NC*H*H'), 5.27 (d, 1H, J 16.4 Hz, NCH*H*'), 7.78 (s, 1H, HAr), 7.80 (s, 1H, HAr); δ_C (100 MHz, $CDCl_3$): 13.7 (CH_3), 13.9 (CH_3), 13.9 (CH_3), 14.0 (CH_3), 14.1 (CH_3), 17.0 (CH_2, C4), 25.5 (CH_2, C5), 31.8 (CH_2, C3), 36.0 (CH_2), 45.7 (CH_2), 57.6 (CH, C6), 62.0 (CH_2, OCH_2), 62.1 (CH_2, OCH_2), 62.3 (CH_2, OCH_2), 62.3 (CH_2, OCH_2), 62.5 (CH_2, OCH_2), 130.8 (CHAr), 130.9 (CAr), 131.0 (CAr), 131.3 (CAr), 131.4 (CAr), 133.6 (CAr), 133.8 (CAr), 134.1 (CHAr),135.4 (CAr), 136.4 (CAr), 137.8 (CAr), 138.0 (CAr), 164.5 (C=O), 164.6 (C=O), 165.5 (C=O), 165.6 (C=O), 166.3 (C=O), 166.5 (C=O), 166.7 (C=O), 166.8 (C=O), 170.7 (C=O); ν_{max}/cm^{-1} (neat) 2984, 2940, 2908, 1722 (C=O), 1695 (C=O), 1445, 1416, 1367, 1234, 1196, 1178, 1155, 1101, 1018; m/z (AP+) 856 ($[M+H]^+$, 100%); HMRS calc. for $C_{43}H_{57}N_2O_{17}$ 873.3652, found 873.3650 $[M+NH_4]^+$.

***Dimethyl 4-oxo-2,3,4,6,11,11a-hexahydro-1H-pyrido[1,2-b]isoquinoline-8,9-dicarboxylate* 2.117b**



R_f 0.20 (ethyl acetate); δ_H (400 MHz, $CDCl_3$): 1.72-1.80 (m, 2H, H2,H1), 1.88-1.96 (m, 1H, H2'), 2.11-2.18 (m, 1H, H1'), 2.40-2.53 (m, 2H, H3/H3'), 2.81-2.94 (m, 2H, H11/H11'), 3.59-3.65 (m, 1H, H11a), 3.88 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.25 (d, 1H, *J* 18.3 Hz, H6), 5.37 (d, 1H, *J* 18.3 Hz, H6'), 7.46 (s, 1H, HAr), 7.50 (s, 1H, HAr); δ_C (100 MHz, $CDCl_3$): 18.5 (CH_2, C2), 29.1 (CH_2, C1), 32.7 (CH_2, C3), 36.6 (CH_2, C11), 44.6 (CH_2, C6), 52.7 (CH_3), 53.0 (CH, C11a), 127.3 (CHAr), 129.0 (CHAr), 130.1 (CAr), 130.2 (CAr), 136.4 (CAr), 137.3 (CAr), 167.7 (C=O), 167.9 (C=O), 169.8 (C=O); ν_{max}/cm^{-1} (neat) 2954, 2936, 1712 (C=O), 1639 (C=O), 1438, 1279, 1237, 1131; m/z (AP+) 318 ($[M+H]^+$, 100%); HMRS calc. for $C_{17}H_{20}O_5N$ 318.1336, found 318.1340 $[M+H]^+$.

***1,6-Di(benzyl-1,2,3,4-tetracarboxylic acid tetramethyl ester)-piperidin-2-one* 2.118b**

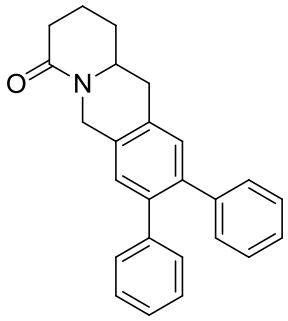


R_f 0.3 (ethyl acetate); δ_H (400 MHz, $CDCl_3$): 1.93-2.03 (m, 2H, H5/H5'), 2.07-2.13 (m, 1H, H4), 2.25-2.37 (m, 1H, H4'), 2.77-2.93 (m, 2H, H3/H3'), 3.14 (dd, 1H, *J* 10.3 and 13.7 Hz, CC*H*H'), 3.54 (dd, 1H, *J* 4.3 and 13.7 Hz, CCH*H*'), 3.94-4.01 (m, 1H, H6), 4.13 (s, 3H, OCH_3), 4.18 (s, 3H, OCH_3), 4.19 (s, 3H, OCH_3), 4.22 (s, 3H, OCH_3), 4.22 (s, 3H, OCH_3), 4.24 (s, 3H, OCH_3), 4.24 (s, 3H, OCH_3), 4.57 (d, 1H, *J* 16.2 Hz, NC*H*H'), 5.64 (d, 1H, *J* 16.2 Hz, NCH*H*'),

8.23 (s, 1H, HAr), 8.25 (s, 1H, HAr); δ_C (100 MHz, $CDCl_3$): 17.0 (CH_2, C4), 25.6 (CH_2, C5), 31.8 (CH_2, C3), 36.1 (CH_2), 45.7 (CH_2), 52.2 (OCH_3), 53.1 (OCH_3), 53.1 (OCH_3), 53.1(OCH_3), 53.2 (OCH_3), 53.2 (OCH_3), 53.3 (OCH_3), 57.6 (CH, C6), 130.4 (CAr), 130.5 (CAr), 130.7 (CAr), 130.7 (CAr), 131.7 (CHAr), 134.0 (CAr), 134.2 (CAr), 134.5 (CHAr), 135.8 (CAr), 136.8 (CAr), 138.0 (CAr), 138.2 (CAr), 164.6 (C=O), 164.8 (C=O), 165.6 (C=O), 165.7 (C=O), 166.8 (C=O), 167.0 (C=O), 167.3 (C=O), 167.4 (C=O), 170.7 (C=O); ν_{max}/cm^{-1} (neat) 2954, 1724 (C=O), 1642 (C=O), 1439, 1330, 1239, 1200, 1156, 1106; m/z (AP+) 85 (100%), 121 (85%), 744 ($[M+H]^+$, 30%); HMRS calc. for $C_{35}H_{41}N_2O_{17}$ 761.2400, found 761.2398 $[M+NH_4]^+$.

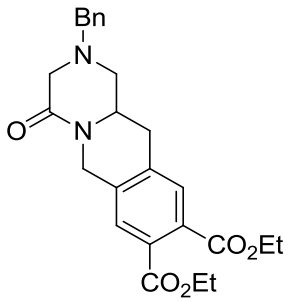
8,9-Diphenyl-2,3,11,11a-tetrahydro-1H-pyrido[1,2-b]isoquinolin-4(6H)-one

2.117g



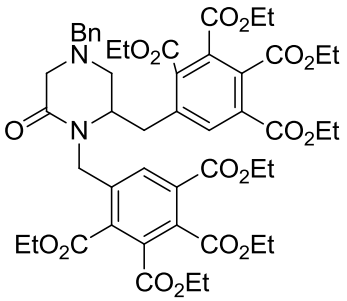
R_f 0.36 (ethyl acetate); δ_H (400 MHz, $CDCl_3$): 1.75-1.84 (m, 2H, H2,H1), 1.93-1.96 (m, 1H, H2'), 2.13-2.21 (m, 1H, H1'), 2.49-2.52 (m, 2H, H3/H3'), 2.86 (dd, 1H, *J* 15.7 and 3.4 Hz, H11), 2.97 (dd, 1H, *J* 15.7 and 11.4 Hz, H11'), 3.69-3.76 (m, 1H, H11a), 4.35 (d, 1H, *J* 17.6 Hz, H6), 5.39 (d, 1H, *J* 17.6 Hz, H6'), 7.09-7.12 (m, 4H, HAr), 7.18-7.22 (m, 8H, HAr); δ_C (100 MHz, $CDCl_3$): 18.7 (CH_2, C2), 29.3 (CH_2, C1), 32.8 (CH_2, C3), 36.5 (CH_2, C11), 44.8 (CH_2, C6), 53.6 (CH, C11a), 126.5 (CHAr), 126.6 (CHAr), 127.9 (CHAr), 127.9 (CHAr), 128.6 (CHAr), 129.8 (CHAr), 130.3 (CHAr), 132.2 (CAr), 133.0 (CAr), 138.9 (CAr), 139.1 (CAr), 140.9 (CAr), 141.1 (CAr), 169.8 (C=O); ν_{max}/cm^{-1} (neat) 2980, 2952, 1732 (C=O), 1634 (C=O), 1446, 1418, 1340, 1264; m/z (AP+) 354 ($[M+H]^+$, 100%); HMRS calc. for $C_{25}H_{22}ON$ 352.1696, found 352.1701 $[M-H]^+$.

***Diethyl 2-benzyl-4-oxo-2,3,4,6,11,11a-hexahydro-1H-pyrazino[1,2-b]isoquinoline-8,9-dicarboxylate* 1.119a**



R_f 0.28 (ethyl acetate); δ_H (400 MHz, $CDCl_3$): 1.34 (t, 3H, *J* 7.1 Hz, CH_3), 1.35 (t, 3H, *J* 7.1 Hz, CH_3), 2.61 (dd, 1H, *J* 5.0 and 11.8, H1), 2.71 (dd, 1H, *J* 3.1 and 16.3 Hz, H11), 2.88 (dd, 4.4 and 11.8 Hz, H1'), 3.11-.3.17 (m, 1H, H11'), 3.19 (d, 1H, *J* 16.1 Hz, H3), 3.28 (d, 1H, *J* 16.1 Hz, H3'), 3.53 (d, 1H, *J* 12.9 Hz, C*H*H'Ph), 3.60 (d, 1H, *J* 12.9 Hz, CH*H*'Ph), 3.61-3.67 (m, 1H, H11a), 4.21 (d, 1H, *J* 18.0 Hz, H6), 4.33 (q, 2H, *J* 7.1 Hz, OCH_2), 4.34 (q, 2H, *J* 7.1 Hz, OCH_2), 5.40 (d, 1H, *J* 18.0 Hz, H6'), 7.26-7.36 (m, 5H, HAr), 7.45 (s, 1H, HAr), 7.49 (s, 1H, HAr); δ_C (100 MHz, $CDCl_3$): 14.1 (CH_3), 34.1 (CH_2, C11), 43.9 (CH_2, C6), 52.1 (CH, C11a), 54.1 (CH_2, C1), 57.8 (CH_2, C3), 61.6 (CH_2Ph), 61.7 (OCH_2), 127.2 (CHAr), 127.7 (CHAr), 128.6 (CHAr), 130.0 (CHAr), 129.3 (CHAr), 130.4 (CAr), 130.6 (CAr), 135.5 (CAr), 136.8 (CAr), 137.0 (CAr), 166.8 (C=O), 167.2 (C=O), 167.4 (C=O); ν_{max}/cm^{-1} (neat) 3055, 2988, 1725 (C=O), 1650 (C=O), 1421, 1264; m/z (AP+) 437 ($[M+H]^+$, 100%); HMRS calc. for $C_{25}H_{28}O_5N_2$ 437.2071, found 437.2065 $[M+H]^+$.

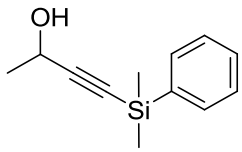
***1,6-Di-1,2,3,4-tetracarboxylic acid tetraethyl ester)-4-benzylpiperazin-2-one* 2.120a**



R_f 0.53 (ethyl acetate); δ_H (400 MHz, $CDCl_3$): 1.19-1.25 (m, 24H, CH_3), 2.37 (dd, 1H, *J* 3.1 and 12.2 Hz, H5), 2.63 (d, 1H, *J* 12.2 Hz, H5'), 2.77 (d, 1H, *J* 16.9 Hz, H3), 3.12-3.21 (m, 2H, CCHH'), 3.26 (d, 1H, *J* 12.8 Hz, C*H*H'Ph), 3.36 (d, 1H, *J* 16.9 Hz, H3'), 3.42-3.44 (m 1H, H6), 3.64 (d, 1H, *J* 12.8 Hz, CH*H*'Ph), 4.15-4.28 (m, 17H, OCH_2/NC*H*H'), 5.23 (d, 1H, J 16.6 Hz, NCH*H*'), 7.15-7.22 (m, 5H, HAr), 7.71 (s, 1H, HAr), 7.87 (s, 1H, HAr); δ_C (100 MHz, $CDCl_3$): 13.7 (CH_3), 13.9 (CH_3), 13.9 (CH_3), 14.0 (CH_3), 14.1 (CH_3), 35.8 (CH_2), 45.3 (CH_2), 52.1 (CH_2, C5), 56.5 (CH_2, C3), 56.9 (CH, C6), 61.7 (CH_2, CH_2Ph), 62.0 (OCH_2), 62.1 (OCH_2), 62.1 (OCH_2), 62.2 (OCH_2), 62.2 (OCH_2), 62.4 (OCH_2), 62.5 (OCH_2), 127.8 (CHAr), 128.5 (CHAr), 129.1 (CHAr), 130.6 (CHAr), 130.8 (CAr), 130.9 (CAr), 131.4 (CAr), 131.7 (CAr), 133.8 (CAr), 133.9 (CAr), 134.9 (CHAr), 135.3 (CAr), 136.1 (CAr), 136.3 (CAr), 137.3 (CAr), 138.0 (CAr), 164.4 (C=O), 164.5 (C=O), 165.5 (C=O), 165.6 (C=O), 166.1 (C=O), 166.4 (C=O), 166.7 (C=O), 166.8 (C=O), 167.8 (C=O;. ν_{max}/cm^{-1} (neat) 2983, 2936, 1723 (C=O), 1658 (C=O), 1465, 1196, 1178, 1155, 1102, 1019; m/z (ES+) 947 ($[M+H]^+$, 100%); HMRS calc. for $C_{49}H_{59}O_{17}N_2$ 947.3808, found 947.3821 $[M+H]^+$.

6.3 Experimental procedures for chapter 3

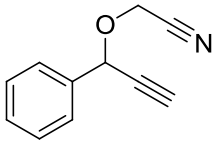
4-(Dimethyl(phenyl)silyl)but-3-yn-2-ol 3.56



Following the procedure of Brawn and co-workers:[157] ^{n}BuLi (3.4 mL of 2.5 M solution in hexane, 8.56 mmol,) was added to a stirred solution of but-3-yn-2-ol **3.55** (300 mg, 4.28 mmol) and dry LiCl (42 mg, 12.9 mmol) in THF (6.0 mL), at -78 ºC under nitrogen. After 1 h, DMPSCl (741 μL, 753 mg, 4.28 mmol) was added dropwise and the reaction was stirred overnight, warming slowly to room temperature. The reaction mixture was quenched with an aq. sat. solution of NH_4Cl (6 mL), extracted with ethyl acetate (3 × 6 mL), dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (hexane/ethyl acetate 9:1) to yield **3.56** (482 mg, 55%) as a clear oil.

R_f 0.29 (hexane/ethyl acetate 4:2); δ_H (500 MHz, $CDCl_3$): 0.54 (s, 6H, CH_3), 1.54 (d, 3H, *J* 6.6 Hz, CH_3), 3.53 (brs, 1H, OH), 4.61 (q, 1H, *J* 6.6 Hz, H2), 7.45-7.48 (m, 3H, HAr), 7.75-7.76 (m, 2H, HAr); δ_C (126 MHz, $CDCl_3$): -0.5 (CH_3), 24.5 (CH_3), 58.9 (CH, C2), 86.5 (C, C≡C), 110.0 (C, C≡C), 128.3 (CHAr), 129.8 (CHAr), 134.0 (CHAr), 137.1 (CAr). Data in agreement with literature.[157]

2-((1-Phenylprop-2-yn-1-yl)oxy)acetonitrile 3.53

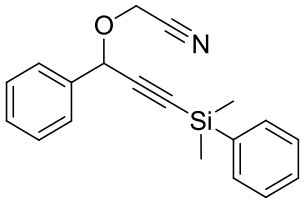


NaH (184 mg of a 60% dispersion in oil, 4.60 mmol) was added to a stirred solution of 1-phenylprop-2-yn-1-ol **3.58** (304 mg, 2.30 mmol) in THF (5.0 mL) at 0 ºC under nitrogen. After 1 h, the temperature was cooled to -20 ºC and bromoacetonitrile (352 μL, 607 mg, 5.06 mmol) was added very slowly and the reaction mixture stirred for 3 h at -20 ºC. Further NaH (184 mg of a 60% dispersion in oil, 4.60 mmol) and bromoacetonitrile (352 μL, 607 mg, 5.06

mmol) were added and the reaction stirred overnight at room temperature. The reaction was quenched with an aq. sat. solution of NH_4Cl (5 mL), extracted with ethyl acetate (3 × 5 mL), dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (hexane/ethyl acetate 4:1) to yield **3.53** (215 mg, 55 %) as a yellow oil.

R_f 0.43 (hexane/ethyl acetate 4:1); δ_H (500 MHz, $CDCl_3$): 2.78 (d, 1H, *J* 2.4 Hz, H3), 4.31 (d, 1H, *J* 16.1 Hz, OC*H*H'), 4.45 (d, 1H, *J* 16.1 Hz, OCH*H*'), 5.39 (d, 1H, *J* 2.4 Hz, H1), 7.38-7.42 (m, 3H, HAr), 7.51-7.53 (m, 2H, HAr); δ_C (126 MHz, $CDCl_3$): 53.2 (CH_2, OCH_2), 71.9 (CH, C1), 78.5 (CH, C≡CH), 79.2 (C, C≡C), 115.9 (C, C≡N), 127.9 (CHAr), 129.1 (CHAr), 129. 7 (CHAr), 136.1 (CAr). ν_{max}/cm^{-1} (neat) 3286, 3067, 3035, 2920, 2861, 2118, 1664, 1608, 1454, 1070; m/z (AP+) 170 ($[M-H]^+$, 20%), 114 (100%); HRMS calc. for $C_{11}H_8NO$ 170.0600, found 170.0597 $[M-H]^+$.

2-((3-(Dimethyl(phenyl)silyl)-1-phenylprop-2-yn-1-yl)oxy)acetonitrile **3.59**

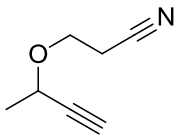


LHMDS (785 μL of a 1.0 M solution in THF, 0.78 mmol) was added to a stirred solution of alkynenitrile **3.53** (133 mg, 0.78 mmol) in THF (1.5 mL), at -78 ºC under nitrogen. After 15 minutes, DMPSCl (132 μL, 134 mg, 0.78 mmol) was added dropwise and the reaction mixture stirred for 15 minutes at -78 ºC. The reaction mixture was quenched with an aq. sat. solution of NH_4Cl (5 mL), extracted with ethyl acetate (3 × 5 mL), dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (hexane/ethyl acetate 9:1) to yield **3.59** (157 mg, 66%) as a colourless oil.

R_f 0.47 (hexane/ethyl acetate 19:1); δ_H (500 MHz, $CDCl_3$): 0.56 (s, 6H, CH_3), 4.37 (d, 1H, *J* 16.0 Hz, OC*H*H'), 4.53 (d, 1H, *J* 16.0 Hz, OCH*H*'), 5.51 (s, 1H, H1), 7.43-7.49 (m, 6H, HAr), 7.59-7.61 (m, 2H, HAr), 7.69-7.71 (m, 2H, HAr); δ_C (126 MHz, $CDCl_3$): -0.78 (CH_3), 53.2 (CH_2, OCH_2), 72.7 (CH, C1), 94.2 (C, C≡C), 102.0 (C, C≡C), 116.1 (C, C≡N), 128.2 (CHAr), 128.4 (CHAr), 129.1

(CHAr), 129.6 (CHAr), 130.0 (CHAr), 134.0 (CHAr), 136.3 (CAr), 136.3 (CAr). ν_{max}/cm^{-1} (neat) 3069, 2961, 2174, 1643, 1428, 1250, 1071; m/z (AP+) 265 (25%), 249 (100%); HRMS calc. for $C_{19}H_{23}NOSi$ 323.1574, found 323.1577 $[M+NH_4]^+$.

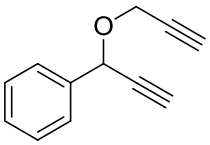
***3-(But-3-yn-2-yloxy)propanenitrile* 3.60**



DBU (500 μL, 505 mg, 3.32 mmol) was added dropwise to a stirred solution of but-3-yn-2-ol **3.55** (1.2 g, 16.59 mmol) in acrylonitrile (4.4 mL, 3.52 g, 66.4 mmol). After 1 h, the acrylonitrile was evaporated and the residue was purified by flash column chromatography (hexane/ethyl acetate 4:1) to yield alkynenitrile **3.60** (1.8 g, 89%) as a colourless oil.

R_f 0.39 (hexane/ethyl acetate 7:3); δ_H (500 MHz, $CDCl_3$): 1.45 (d, 1H, *J* 6.6 Hz, CH_3), 2.46 (d, 1H, *J* 2.0 Hz, H4), 2.62 (t, 2H, *J* 6.5 Hz, $CH_2C{\equiv}N$), 3.61 (dt, 1H, *J* 6.5 and 9.3 Hz, OC*H*H'), 3.93 (dt, 1H, *J* 6.5 and 9.3 Hz, OCH*H*'), 4.22 (dq, 1H, *J* 2.0 and 6.6 Hz, H2); δ_C (126 MHz, $CDCl_3$): 19.1 (CH_2), 22.1 (CH_3), 63.3 (CH_2, OCH_2), 65.9 (CH, C2), 74.0 (CH, C≡CH), 82.9 (C, C≡C), 117.9 (C, C≡N); ν_{max}/cm^{-1} (neat) 3284, 2990, 2939, 2883, 2253, 2111, 1374, 1328, 1105; m/z (AP+) 124 ($[M+H]^+$, 100%); HRMS calc. for $C_7H_{10}NO$ 124.0757, found 124.0754 $[M+H]^+$.

(1-(Prop-2-yn-1-yloxy)prop-2-yn-1-yl)benzene 3.63

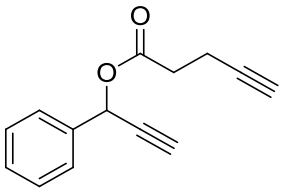


NaH (631 mg of a 60% dispersion in oil, 15.78 mmol,) was added to a stirred solution of 1-phenylprop-2-yn-1-ol **3.58** (1.6 g, 12.14 mmol) in THF (36 mL) at 0 ºC under nitrogen. After 1 h, propargyl bromide **2.9** (1.8 mL of a 80% solution in toluene, 15.78 mmol) was added dropwise and the reaction stirred for 3 h at 0

ºC. The reaction was quenched with an aq. sat. solution of NH_4Cl (40 mL), extracted with ethyl acetate (3 × 40 mL), dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (hexane/ethyl acetate 4:1) to yield **3.63** (829 mg, 40%) as a pale yellow oil.

R_f 0.44 (hexane/ethyl acetate 4:1); δ_H (500 MHz, $CDCl_3$): 2.50 (t, 1H, *J* 2.4 Hz, C≡CH) 2.69 (d, 1H, *J* 2.2 Hz, H3), 4.30 (dd, 1H, *J* 2.4 and 15.7 Hz, OC*H*H'), 4.41 (dd, 1H, *J* 2.4 and 15.7 Hz, OCH*H*'), 5.45 (d, 1H, *J* 2.2 Hz, H1), 7.35-7.42 (m, 3H, HAr), 7.56 (brd, 2H, *J* 7.2 Hz, HAr); δ_C (126 MHz, $CDCl_3$): 55.7 (CH, C1), 70.0 (CH_2, OCH_2), 75.4 (CH, C≡CH), 76.5 (CH, C≡CH), 79.3 (C, C≡C), 80.9 (C, C≡C), 127.8 (CHAr), 128.8 (CHAr), 129.0 (CHAr), 137.6 (CAr). Data in agreement with literature.[206]

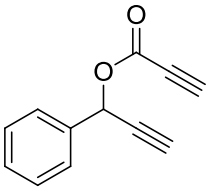
***1-Phenylprop-2-yn-1-yl pent-4-ynoate* 3.70**



DMAP (19 mg, 0.15 mmol) and NEt_3 (323 μL, 234 mg, 2.32 mmol) were added to a stirred solution of 1-phenylprop-2-yn-1-ol **3.58** (204 g, 1.54 mmol) in DCM (2.0 mL) at 0 ºC under nitrogen. Pent-4-ynoyl chloride (270 mg, 2.32 mmol) was then added very slowly and the reaction mixture was stirred at 0 ºC for 1.5 h. The solvent was removed under vacuum and the residue purified by flash column chromatography (hexane/ethyl acetate 9:1) to yield ester **3.70** (280 mg, 85%) as a colourless oil.

R_f 0.34 (hexane/ethyl acetate 4:1); δ_H (500 MHz, $CDCl_3$): 1.96 (t, 1H, *J* 2.0 Hz, C≡CH), 2.51-2.54 (m, 2H, CH_2C≡C), 2.56-2.66 (m, 2H, COCHH'), 2.67 (d, 1H, *J* 1.9 Hz, H3), 6.49 (d, 1H, *J* 1.9 Hz, H1), 7.36-7.41 (m, 3H, HAr), 7.53-7.55 (m, 2H, HAr); δ_C (126 MHz, $CDCl_3$): 14.5 (CH_2), 33.5 (CH_2, OCH_2), 65.8 (CH, C1), 69.5 (CH, C≡CH), 75.9 (CH, C≡CH), 80.3 (C, C≡C), 82.3 (C, C≡C), 127.9 (CHAr), 128.9 (CHAr), 129.4 (CHAr), 136.5 (CAr), 170.7 (CO); ν_{max}/cm^{-1} (neat) 3303, 3055, 1741 (C=O), 1421, 1371, 1264, 1155; m/z (AP+) 213 ($[M+H]^+$, 25%), 120 (100%), 115 (95%); HRMS calc. for $C_{14}H_{13}O_2$ 213.0910, found 213.0910 $[M+H]^+$, $C_{14}H_{16}NO_2$ 230.1176, found 230.1171 $[M+NH_4]^+$.

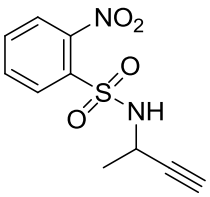
***1-Phenylprop-2-yn-1-yl propiolate* 3.74**



Triphenylphosphine (2.15 g, 8.19 mmol) and propiolic acid (378 μL, 430 mg, 6.14 mmol) were added to a stirred solution of 1-phenylprop-2-yn-1-ol **3.58** (541 mg, 4.09 mmol) in THF (14 mL) under nitrogen. The reaction mixture was cooled to 0 ºC and DEAD (1.3 mL, 1.4 g, 8.19 mmol) was added very slowly. After 2 h, the solvent was removed under vacuum, diethyl ether was added and the solution was kept in the fridge overnight. The white solid was filtered off, the filtrate was concentrated under vacuum and purified by flash column chromatography (hexane/ethyl acetate 9:1) to yield product **3.74** (436 mg, 58%) as a white solid.

R_f 0.31 (hexane/ethyl acetate 4 :1) ; mp = 49-52 ºC ; δ_H (500 MHz, $CDCl_3$): 2.78 (d, 1H, *J* 2.1 Hz, H3), 2.97 (s, 1H, C≡CH), 6.52 (d, 1H, *J* 2.1 Hz, H1), 7.40-7.45 (m, 3H, HAr), 7.57-7.59 (m, 2 H, HAr); δ_C (126 MHz, $CDCl_3$): 67.5 (CH, C1), 74.3 (C, C≡C), 76.7 (CH, C≡CH), 77.1 (CH, C≡CH), 79.3 (C, C≡C), 128.2 (CHAr), 129.1 (CHAr), 129.8 (CHAr), 135.5 (CAr), 151.7 (CO); ν_{max}/cm^{-1} (neat) 3275, 3263, 3073, 2959, 2115, 1705 (C=O), 1222, 1192, 1177; m/z (AP+) 184 $[M]^+$, 5%; 120 (35%), 114 (100%); HRMS calc. for $C_{12}H_9O_2$ 185.0597, found 185.0596 $[M+H]^+$.

***N-(But-3-yn-2-yl)-2-nitrobenzenesulfonamide* 3.77**



From but-3-yn-2-amine hydrochloride 3.28

To a stirred solution of but-3-yn-2-amine hydrochloride **3.75** (243 mg, 3.52 mmol) and NEt_3 (1.5 mL, 1.1 g, 10.55 mmol) in DCM (2.0 mL) at room temperature was added nosyl chloride (1.2 g, 5.27 mmol). The reaction was

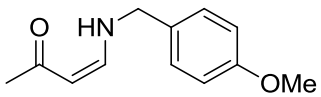
stirred for 24 h at 40 ºC, then it was quenched with water (5 mL), extracted with ethyl acetate (3 × 5 mL), dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (hexane/ethyl acetate 1:0 to 4:1) affording amine **3.77** (355 mg, 96%) as a white solid.

From *tert*-butyl but-3-yn-2-yl((2-nitrophenyl)sulfonyl)carbamate 3.85

Tert-butyl but-3-yn-2-yl((2-nitrophenyl)sulfonyl)carbamate **3.85** (1.1 g, 3.10 mmol) was stirred in TFA (8.6 mL, 12.8 g, 112 mmol) for 5 minutes and then neutralized by pouring into an aq. sat. solution of $NaHCO_3$. The reaction mixture was extracted with ethyl acetate (3 × 200 mL), the combined organic phases were dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (hexane/ethyl acetate 7:3) to afford amine **3.77** (711 mg, 90%) as a white solid.

R_f 0.32 (hexane/ethyl acetate 7:3); mp = 107-109 ºC ; δ_H (500 MHz, $CDCl_3$): 1.51 (d, 3H, *J* 7.0 Hz, CH_3), 2.00 (d, 1H, *J* 2.2 Hz, H4), 4.32-4.39 (m, 1H, H2), 5.67 (d, 1H, *J* 9.4 Hz, NH), 7.75-7.78 (m, 2H, HAr), 7.90-7.92 (m, 1H, HAr), 8.18-8.22 (m, 1H, HAr); δ_C (126 MHz, $CDCl_3$): 23.2 (CH_3), 42.1 (CH, C2), 72.6 (CH, C≡CH), 82.1 (C, C≡C), 125.7 (CHAr), 131.8 (CHAr), 133.1 (CHAr), 134.1 (CHAr), 134.2 (CAr), 148.1 (CAr); ν_{max}/cm^{-1} (neat) 3307, 3267, 3097, 2996, 2944, 2880, 2110, 1535, 1412, 1357, 1335, 1303, 1163, 1118; m/z (AP+) 255 ($[M+H]^+$, 100%); HRMS calc. for $C_{10}H_{11}N_2O_4S$ 255.0434, found 255.0436 $[M+H]^+$.

***(Z)-4-((4-Methoxybenzyl)amino)but-3-en-2-one* 3.90**

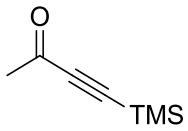


But-3-yn-2-one **3.78** (115 μL, 100 mg, 1.47 mmol) was added to a stirred solution of PMB amine (254 μL, 267 mg, 1.62 mmol) in DCM (5.0 mL) under nitrogen. After 30 minutes, $NaBH_3CN$ (129 mg, 2.06 mmol) was added portionwise and the reaction was stirred overnight at room temperature. The reaction was then quenched with an aq. sat. solution of $NaHCO_3$ (3 mL), followed by NH_4Cl (3 mL). The reaction mixture was extracted with DCM (3 × 5

mL), and the combined organic layers dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (hexane/ethyl acetate 1:1) to afford keto-enamine **3.80** (121 mg, 40%) as a brown oil.

R_f 0.18 (hexane/ethyl acetate 1:1); δ_H (400 MHz, $CDCl_3$): 2.04 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.30 (d, 2H, *J* 5.6 Hz, CH_2), 5.02 (d, 1H, *J* 7.4 Hz, H3), 6.69 (dd, 1H, *J* 7.4 and 12.8 Hz, H4), 6.86 (d, 2H, *J* 8.7 Hz, HAr), 7.16 (d, 2H, *J* 8.7 Hz, HAr), 9.99 (brs, 1H, NH); δ_C (126 MHz, $CDCl_3$): 29.1 (CH_3), 52.0 (CH_2), 55.3 (OCH_3), 94.3 (CH, C3), 114.2 (CHAr), 128.6 (CHAr), 129.9 (CAr), 152.3 (CH, C4), 159.1 (CAr), 197.7 (C=O); ν_{max}/cm^{-1} (neat) 3225, 3020, 2957, 2935, 2897, 2847, 1613 (C=O), 1575, 1532, 1510, 1242; m/z (AP+) 206 ($[M+H]^+$, 80%), 121 (100%); HRMS calc. for $C_{12}H_{16}NO_2$ 206.1176, found 206.1176 $[M+H]^+$.

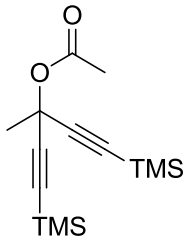
4-(Trimethylsilyl)but-3-yn-2-one 3.83



Following the procedure of Holeman and co-workers:[165] Trimethylsilylacetylene (719 μL, 500 mg, 5.09 mmol) was added dropwise to a stirred solution of ethylmagnesium chloride (2.55 mL of a 2 M solution in THF, 5.09 mmol,) in THF (5.0 mL) at 0 ºC under nitrogen (evolution of ethane gas observed). After 20 minutes acetic anhydride **3.81** (962 μL, 1.0 g, 10.18 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (5 mL) and neutralised with 5% aq. HCl. The organic layer was washed with an aq. sat. solution of $NaHCO_3$ (3×5 mL), dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (hexane/ethyl acetate 19:1) to yield 4-(trimethylsilyl)but-3-yn-2-one **3.83** (90 mg, 13%) as a clear oil and byproduct **3.84** (1.1 g, 75%) as a white solid.

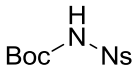
R_f 0.53 (hexane/ethyl acetate 9:1); δ_H (500 MHz, $CDCl_3$): 0.22 (s, 9H, $Si(CH_3)_3$), 2.32 (s, 3H, CH_3); δ_C (126 MHz, $CDCl_3$): -0.6 (CH_3), 32.7 (CH_3), 97.5 (C≡C), 102.6 (C≡C), 184.6 (C=O). Data in agreement with literature.[168]

***3-Methyl-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl acetate* 3.84**



R_f 0.45 (hexane/ethyl acetate 9:1) ; mp = 34-37 ºC ; δ_H (500 MHz, $CDCl_3$): 0.12 (s, 18H, $Si(CH_3)_3$), 1.82 (s, 3H, CH_3), 2.01 (s, 3H, CH_3); δ_C (126 MHz, $CDCl_3$): 0.0 (CH_3), 21.8 (CH_3), 31.2 (CH_3), 64.7 (C), 89.3 (C, C≡C), 102.6 (C, C≡C), 168.1 (C=O); ν_{max}/cm^{-1} (neat) 3007, 2958, 2900, 2185, 1751 (C=O), 1410, 1367, 1249, 1224, 1203; m/z (AP+) 281 ($[M+H]^+$, 60%), 220 (100%); HRMS calc. for $C_{14}H_{25}O_2Si_2$ 281.1388, found 281.1392 $[M+H]^+$.

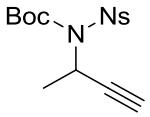
***tert*-Butyl (2-nitrophenyl)sulfonylcarbamate**



Following the procedure of Fukuyama and co-workers:[207] Boc_2O (2.7 g, 12.34 mmol) was added to a stirred solution of 2-nitrobenzenesulfonamide (2.1 g, 10.29 mmol) and NEt_3 (2.2 mL, 1.6 g, 15.43 mmol) in DCM (22 mL) at room temperature under nitrogen. DMAP (126 mg, 1.03 mmol) was added and after 30 minutes the reaction mixture was quenched with an aq. sat. solution of NH_4Cl. The organic phase was extracted with diethyl ether (3 × 20 mL), the combined organic layers dried over $MgSO_4$ and concentrated under vacuum to yield *tert*-butyl (2-nitrophenyl)sulfonylcarbamate (3.0 g, 97%) as a white solid.

R_f 0.61 (ethyl acetate/hexane 1:1) ; mp = 191-193 ºC [lit.[208] 194-196 ºC]; δ_H (400 MHz, $CDCl_3$): 1.43 (s, 9H, CH_3), 7.57 (brs, 1H, NH), 7.79-7.81 (m, 2H, HAr), 7.86-7.87 (m, 1H, HAr), 8.33-8.37 (m, 1H, HAr); δ_C (101 MHz, $CDCl_3$): 27.9 (CH_3), 84.8 (C), 125.1 (CHAr), 132.4 (CHAr), 133.3 (CHAr), 134.7 (CHAr), 147.6 (CAr), 150.1 (C=O). Data in agreement with literature.[208]

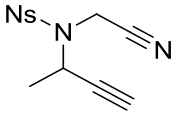
***tert-Butyl but-3-yn-2-yl((2-nitrophenyl)sulfonyl)carbamate* 3.85**



Triphenylphosphine (1.7 g, 6.27 mmol) and *tert*-butyl (2-nitrophenyl)sulfonylcarbamate (1.5 g, 5.02 mmol) were added to a stirred solution of but-3-yn-2-ol **3.55** (293 mg, 4.18 mmol) in THF (14 mL) under nitrogen. The reaction mixture was cooled to 0 ºC and DEAD (993 μL, 1.1 g, 6.27 mmol) was added very slowly. After 2.5 h, a further 0.2 eq of *tert*-butyl (2-nitrophenyl)sulfonylcarbamate (253 mg, 0.84 mmol) and triphenylphosphine (219 mg, 0.84mmol) were added and the reaction mixture stirred for 1 h. The solvent was removed under vacuum, diethyl ether was added and the solution was kept in the fridge overnight. The white solid was filtered off, the filtrate was concentrated under vacuum and purified by flash column chromatography (hexane/ethyl acetate 1:1) to yield **3.85** (1.5 g, 96%) as a white solid.

R_f 0.26 (hexane/ethyl acetate 4:1); mp = 82-84 ºC ; δ_H (400 MHz, $CDCl_3$): 1.42 (s, 9H, CH_3), 1.75 (d, 3 H, *J* 7.0 Hz, CH_3), 2.41 (d, 1H, *J* 2.5 Hz, H4), 5.28 (dq, 1H, *J* 2.5 and 7.0 Hz, H2), 7.72-7.81 (m, 3H, HAr), 8.29-8.34 (m, 1H, HAr); δ_C (100 MHz, $CDCl_3$): 21.8 (CH_3), 27.9 (CH_3), 46.0 (CH, C2), 71.4 (C, C≡C), 82.0 (CH, C≡CH), 85.7 (C), 124.6 (CHAr), 132.0 (CHAr), 133.0 (CHAr), 133.7 (CAr), 134.2 (CHAr), 147.9 (CAr), 149.7 (C=O); ν_{max}/cm^{-1} (neat) 3282, 3110, 3082, 2990, 2940, 2122, 1732 (C=O), 1544, 1366, 1251, 1125; m/z (AP+) 355 ($[M+H]^+$, 30%), 299 ($[M-C(CH_3)_3]^+$, 100%); HRMS calc. for $C_{15}H_{19}O_6N_2S$ 355.0958, found 355.0961 $[M+H]^+$.

***N-(But-3-yn-2-yl)-N-(cyanomethyl)-2-nitrobenzenesulfonamide* 3.86**

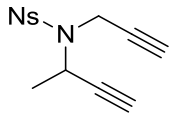


NaH (142 mg of a 60% dispersion in oil, 3.56 mmol,) was added to a stirred solution of amine **3.77** (696 mg, 2.74 mmol) in DMF (11 mL), at 0 ºC under nitrogen. After 1 h, 2-bromoacetonitrile (286 μL, 493 mg, 4.11 mmol) was added dropwise and the reaction mixture was stirred for an additional 30 minutes. The

reaction was quenched with an aq. sat. solution of NH_4Cl (20 mL), extracted with ethyl acetate (3 × 20 mL), the combined organic layers were dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (hexane/ethyl acetate 7:3) to yield **3.86** (743 mg, 93%) as a yellow oil.

R_f 0.32 (ethyl acetate/hexane 2:3); δ_H (500 MHz, $CDCl_3$): 1.62 (d, 3H, *J* 7.0 Hz, CH_3), 2.43 (d, 1H, *J* 2.0 Hz, H4), 4.34 (d, 1H, *J* 18.5 Hz, NC*H*H'), 4.47 (d, 1H, *J* 18.5 Hz, NCH*H*'), 4.95 (dq, 1H, *J* 2.0 and 7.0 Hz, H2), 7.73-7.80 (m, 3H, HAr), 8.10-8.12 (dd, 1H, J 1.6 and 7.3 Hz, HAr); δ_C (126 MHz, $CDCl_3$): 21.6 (CH_3), 32.0 (CH_2), 47.1 (CH, C2), 75.6 (CH, C≡CH), 79.6 (C, C≡C), 115.9 (C, C≡N), 125.1 (CHAr), 131.5 (CHAr), 132.1 (CAr), 132.7 (CHAr), 135.0 (CHAr), 148.2 (CAr); ν_{max}/cm^{-1} (neat) 3288, 3003, 2964, 2944, 2116, 1541, 1372, 1350, 1335, 1156; m/z (AP+) 294 ($[M+H]^+$, 100%); HRMS calc. for $C_{12}H_{11}N_3O_4SNa$ 316.0362, found 316.0364 $[M+Na]^+$.

***N-(But-3-yn-2-yl)-2-nitro-N-(prop-2-yn-1-yl)benzenesulfonamide* 3.89**

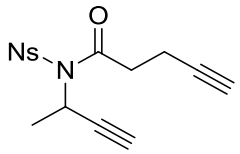


NaH (82 mg of a 60% dispersion in oil, 2.05 mmol) was added to a stirred solution of amine **3.77** (401 mg, 1.58 mmol) in DMF (6.6 mL), at 0 ºC under nitrogen. After 1 h propargyl bromide (527 μL of an 80% solution in toluene, 4.73 mmol) was added dropwise and the reaction mixture stirred for 7.5 h. The reaction was quenched with an aq. sat. solution of NH_4Cl (10 mL), extracted with ethyl acetate (3 × 10 mL), and the combined organic layers dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (hexane/ethyl acetate 4:2) to yield **3.89** (418 mg, 91%) as a yellow oil.

R_f 0.35 (ethyl acetate/hexane 7:3); δ_H (400 MHz, $CDCl_3$): 1.63 (d, 3H, *J* 7.0 Hz, CH_3), 2.19 (t, 1H, *J* 2.5 Hz, C≡CH), 2.35 (d, 1H, *J* 2.3 Hz, H4), 4.18 (dd, 1H, *J* 2.5 and 18.6 Hz, NC*H*H'), 4.35 (dd, 1H, *J* 2.5 and 18.6 Hz, NCH*H*'), 4.94 (dq, 1H, *J* 2.3 and 7.0 Hz, H2), 7.67-7.74 (m, 3H, HAr), 8.11-8.14 (dd, 1H, J 1.6 and 7.3 Hz, HAr); δ_C (100 MHz, $CDCl_3$): 22.1 (CH_3), 34.0 (CH_2), 47.0 (CH, C2), 73.3

(CH, C≡CH), 74.2 (CH, C≡CH), 74.5 (C, C≡C), 80.9 (C, C≡C), 124.6 (CHAr), 131.2 (CHAr), 132.2 (CHAr), 133.2 (CAr), 134.2 (CHAr), 148.3 (CAr); ν_{max}/cm^{-1} (neat) 3304, 3286, 3096, 2998, 2940, 2918, 2114, 1539, 1445, 1369, 1351, 1338, 1153; m/z (AP+) 293 ([M+H]$^+$, 100%); HRMS calc. for $C_{13}H_{13}N_2O_4S$ 293.0591, found 293.0593 [M+H]$^+$.

***N-(But-3-yn-2-yl)-N-((2-nitrophenyl)sulfonyl)pent-4-ynamide* 3.90**



NaH (40.9 mg of a 60% dispersion in oil, 1.02 mmol) was added to a stirred solution of amine **3.30** (200 mg, 0.79 mmol) in THF (3.0 mL), at 0 ºC under nitrogen. After 1 h pent-4-ynoyl chloride (138 mg, 1.18 mmol) was added and the reaction mixture stirred for 8 h at 0 ºC. The reaction mixture was quenched with an aq. sat. solution of NH_4Cl (5 mL), extracted with DCM (3 × 5 mL), and the combined organic layers dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (hexane/ethyl acetate 4:2) to yield **3.90** (103 mg, 39%) as a colourless oil and RSM **3.77** (90 mg, 45%).

R_f 0.34 (hexane/ethyl acetate 7:3); δ_H (500 MHz, $CDCl_3$): 1.72 (d, 3H, *J* 6.8 Hz, CH_3), 1.95 (t, 1H, *J* 2.7 Hz, C≡CH), 2.39 (d, 1H, *J* 2.5 Hz, H4), 2.50-2.55 (m, 2H, CH_2C≡C), 2.91 (dt, 1H, *J* 17.4 and 7.3 Hz, COC*H*H'), 3.16 (dt, 1H, *J* 17.4 and 7.3 Hz, COCH*H*'), 5.24 (dq, 1H, *J* 2.5 and 6.8 Hz, H2), 7.78-7.81 (m, 2H, HAr), 7.86-7.88 (m, 1H, HAr), 8.30-8.32 (m, 1H, HAr); δ_C (126 MHz, $CDCl_3$): 14.4 (CH_3), 22.0 (CH_2, CH_2C≡CC), 37.1 (CH, C2), 45.8 (CH_2, OCH_2), 69.9 (CH, C≡CH), 73.5 (CH, C≡CH), 81.7 (C, C≡C), 82.4 (C, C≡C), 125.4 (CHAr), 132.9 (CHAr), 133.1 (CHAr), 133.2 (CAr), 135.2 (CHAr), 148.1 (CAr), 171.8 (C=O); ν_{max}/cm^{-1} (neat) 3298, 3275, 3020, 2982, 2941, 2167, 1659 (C=O), 1539, 1421, 1370, 1150; m/z (AP+) 335 ([M+H]$^+$, 100%); HRMS calc. for $C_{15}H_{15}N_2O_5S$ 335.0712, found 335.0714 [M+H]$^+$.

General procedure for the transition-metal catalysed [2+2+2] cyclotrimerisation reactions:

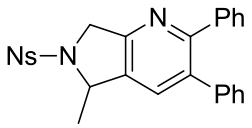
$CpCo(CO)_2$ (11 μL, 15 mg, 0.08 mmol) was added to a stirred solution of amine **3.86** (120 mg, 0.41 mmol) and diphenylacetylene **2.113g** (219 mg, 1.23 mmol) in anhydrous chlorobenzene (2.3 mL, 0.18 M). The reaction was performed in a closed vessel with microwave irradiation at 150 ºC (300 W) for 15 minutes. The solvent was removed under vacuum and the residue purified by flash column chromatography (hexane/ethyl acetate 7:3) to yield bicycle **3.91g** (22 mg, 11%) as a orange oil and RSM **3.86** (54mg, 54%).

The percentage yield and the appearance of the compounds obtained in these cyclotrimerisation reactions are listed below.

Compound No	% yield	mass (mg)	Appearence
3.94	37	62	Dark yellow oil
3.96	6	9	Dark yellow oil
3.97	12	12	Dark yellow oil
3.98	50	46	Yellow oil
3.99	20	20	Brown oil
3.100	29	30	Brown oil
3.101	12	31	Brown oil
3.105	4	14	Yellow oil
3.107g	70	104	Yellow oil
3. 107h	4	5	Yellow oil
3. 107a	12	18	Dark yellow oil
3. 109a	61	141	Brown oil
3. 107i	16	126	Dark yellow oil
3. 109i	21	76	Brown oil
3. 107k	9	15	Yellow oil
3.110g	97	109	Yellow oil
3.110k (1:1 isomer mix.)	8	7	Yellow oil
3.111a	31	34	Yellow oil
3.112a	34	37	Yellow oil
3.111b	30	49	Yellow oil
3.112b	29	48	Yellow oil
3.111d	20	38	Yellow oil
3.112d	21	39	Yellow oil
3.111e	27	50	Yellow oil
3.112e	28	52	Yellow oil
3.112f	28	60	Yellow oil
3.121	15	12	Yellow oil

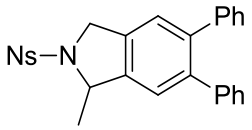
Table XXXVII – Yield and appearance of compounds obtained through the [2+2+2] cyclotrimerisation of alkynes.

***5-Methyl-6-((2-nitrophenyl)sulfonyl)-2,3-diphenyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine* 3.91g**



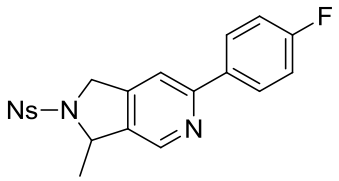
R_f 0.31 (hexane/ethyl acetate 2:3); δ_H (500 MHz, $CDCl_3$): 1.71 (d, 3H, *J* 6.5 Hz, CH_3), 4.86 (d, 1H, *J* 14.6 Hz, H7), 4.90 (dd, 1H, *J* 2.2 and 14.6 Hz, H7'), 5.47 (dq, 1H, *J* 2.2 and 6.5, H5), 7.12-7.15 (m, 2H, HAr), 7.20-7.30 (m, 8H, HAr), 7.53 (s, 1H, HAr), 7.62-7.65 (m, 1H, HAr), 7.67-7.73 (m, 2H, HAr), 8.08-8.10 (m, 1H, HAr); δ_C (126 MHz, $CDCl_3$): 23.9 (CH_3), 54.0 (CH_2, C7), 61.3 (CH, C5), 124.5 (CHAr), 127.7 (CHAr), 128.2 (CHAr), 128.3 (CHAr), 128.7 (CHAr), 129.8 (CHAr), 130.1 (CHAr), 131.1 (CHAr), 131.9 (CHAr), 132.1 (CAr), 133.1 (CHAr), 133.9 (CAr), 134.1 (CHAr), 136.0 (CAr), 139.7 (CAr), 139.7 (CAr), 154.5 (CAr), 158.1 (CAr); ν_{max}/cm^{-1} (neat) 3056, 2988, 2928, 1546, 1432, 1354, 1264, 1167; m/z (AP+) 472 ($[M+H]^+$, 100%); HRMS calc. for $C_{26}H_{22}N_2O_4S$ 472.1326, found 472.1314 $[M+H]^+$.

***1-Methyl-2-((2-nitrophenyl)sulfonyl)-5,6-diphenylisoindoline* 3.94**



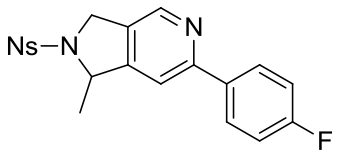
R_f 0.41 (hexane/ethyl acetate 7:3); δ_H (500 MHz, $CDCl_3$): 1.69 (d, 3H, *J* 6.1 Hz, CH_3), 4.90 (dd, 1H, *J* 1.6 and 14.0 Hz, H3), 4.94 (d, 1H, *J* 14.0 Hz, H3'), 5.38 (q, 1H, *J* 6.1, H1), 7.08-7.11 (m, 4H, HAr), 7.19-7.22 (m, 6H, HAr), 7.23 (s, 1H, HAr), 7.28 (s, 1H, HAr), 7.62-7.65 (m, 1H, HAr), 7.68-7.73 (m, 2H, HAr), 8.04-8.07 (m, 1H, HAr); δ_C (126 MHz, $CDCl_3$): 23.8 (CH_3), 53.8 (C3), 62.5 (C1), 124.5 (CHAr), 124.6 (CHAr), 124.8 (CHAr), 127.0 (CHAr), 128.2 (CHAr), 130.0 (CHAr), 130.6 (CHAr), 131.9 (CHAr), 132.5 (CAr), 133.9 (CHAr), 134.1 (CAr), 141.0 (CAr), 141.0 (CAr), 141.1 (CAr), 141.1 (CAr), 141.2 (CAr), 148.8 (CAr); ν_{max}/cm^{-1} (neat) 3104, 3029, 2929, 2854, 1539, 1479, 1371, 1355, 1170; m/z (AP+) 471 $[M+H]^+$, 100%; HRMS calc. for $C_{27}H_{23}N_2O_4S$ 471.1373, found 471.1365 $[M+H]^+$.

***6-(4-Fluorophenyl)-3-methyl-2-((2-nitrophenyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine* 3.6**



R_f 0.47 (hexane/ethyl acetate 1:1); δ_H (400 MHz, $CDCl_3$): 1.65 (d, 3H, *J* 6.3 Hz, CH_3), 4.85 (dd, 1H, *J* 1.8 and 15.2 Hz, H1), 4.94 (d, 1H, *J* 15.2 Hz, H1'), 5.37 (dq, 1H, *J* 1.8 and 6.3, H3), 7.12-7.17 (m, 2H, HAr), 7.56 (s, 1H, H7), 7.63-7.65 (m, 1H, HAr), 7.70-7.73 (m, 2H, HAr), 7.91-7.94 (m, 2H, HAr), 8.05-8.08 (m, 1H, HAr). 8.51 (s, 1H, H4); δ_C (101 MHz, $CDCl_3$): 23.4 (CH_3), 53.3 (CH_2, C1), 60.7 (CH, C3), 114.1 (CHAr, C7), 115.8 (d, *J* 21.6 Hz, CHAr), 124.4 (CHAr), 128.8 (d, *J* 8.4 Hz, CHAr), 130.6 (CHAr), 131.8 (CHAr), 132.2 (CAr), 134.0 (CHAr), 134.9 (d, *J* 3.2 Hz, CAr), 136.0 (CAr), 143.9 (CHAr, C4), 145.3 (CAr), 156.2 (CAr), 162.4 (CAr), 164.9 (CAr); ν_{max}/cm^{-1} (neat) 3083, 2918, 2850, 1614, 1602, 1536, 1513, 1475, 1366, 1339, 1300, 1212, 1157, 1135, 1096; m/z (AP+) 414 ($[M+H]^+$, 100%); HRMS calc. for $C_{20}H_{16}N_3O_4FS$ 414.0918, found 414.0915 $[M+H]^+$.

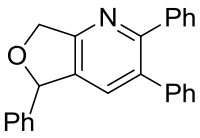
***6-(4-Fluorophenyl)-1-methyl-2-((2-nitrophenyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine* 3.97**



R_f 0.27 (hexane/ethyl acetate 1:1); δ_H (400 MHz, $CDCl_3$): 1.65 (d, 3H, *J* 6.4 Hz, CH_3), 4.83-4.96 (m, 2H, H3, H3'), 5.36 (q, 1H, *J* 6.4, H1), 7.12-7.18 (m, 2H, HAr), 7.49 (s, 1H, H7), 7.62-7.65 (m, 1H, HAr), 7.68-7.75 (m, 2H, HAr), 7.91-7.96 (m, 2H, HAr), 8.05-8.07 (m, 1H, HAr). 8.56 (s, 1H, H4); δ_C (101 MHz, $CDCl_3$): 23.0 (CH_3), 51.7 (CH_2, C3), 62.0 (CH, C1), 113.9 (CHAr, C7), 115.8 (d, *J* 21.6 Hz, CHAr), 124.4 (CHAr), 128.8 (d, *J* 8.4 Hz, CHAr), 129.4 (CAr), 130.6 (CHAr), 131.8 (CHAr), 132.0 (CAr), 134.0 (CHAr), 135.0 (d, *J* 3.1 Hz, CAr), 144.0 (CHAr, C4), 151.7 (CAr), 156.3 (CAr), 162.4 (CAr), 164.9 (CAr); ν_{max}/cm^{-1} (neat) 3075, 2920, 2849, 1614, 1601, 1539, 1487, 1372, 1353, 1341, 1215,

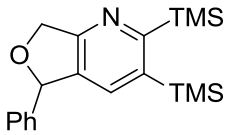
1170, 1125, 1083; m/z (AP+) 414 ($[M+H]^+$, 100%); HRMS calc. for $C_{20}H_{16}N_3O_4FS$ 414.0918, found 414.0915 $[M+H]^+$.

***2,3,5-Triphenyl-5,7-dihydrofuro[3,4-b]pyridine* 3.98**



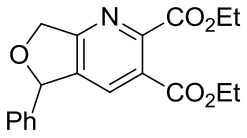
R_f 0.21 (hexane/ethyl acetate 9:1); δ_H (500 MHz, $CDCl_3$): 5.31 (d, 1H, *J* 13.4 Hz, H7), 5.43 (dd, 1H, *J* 1.2 and 13.4 Hz, H7'), 6.32 (s, 1H, H5), 7.11-7.12 (m, 2H, HAr), 7.23-7.26 (m, 6H, HAr), 7.34-7.36 (m, 2H, HAr), 7.39-7.44 (m, 6H, HAr); δ_C (126 MHz, $CDCl_3$): 73.1 (CH_2, C7), 85.1 (CH, C5), 127.0 (CHAr), 127.5 (CHAr), 128.1 (CHAr), 128.2 (CHAr), 128.5 (CHAr), 128.7 (CHAr), 129.0 (CHAr), 129.9 (CHAr), 130.2 (CHAr), 133.0 (CHAr), 134.1 (CAr), 135.4 (CAr), 140.1 (CAr), 140.1 (CAr), 141.5 (CAr), 157.8 (CAr), 159.6 (CAr); ν_{max}/cm^{-1} (neat) 3055, 3030, 2852, 1602, 1556, 1493, 1449, 1429, 1398, 1354, 1038, 1025; m/z (AP+) 350 ($[M+H]^+$, 100%); HRMS calc. for $C_{25}H_{19}NO$ 350.1539, found 350.1537 $[M+H]^+$.

***5-Phenyl-2,3-bis(trimethylsilyl)-5,7-dihydrofuro[3,4-b]pyridine* 3.99**



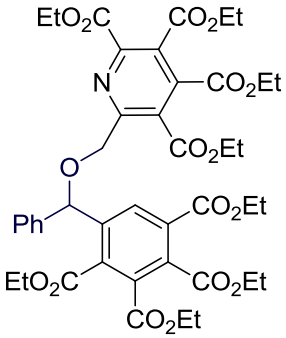
R_f 0.24 (hexane/ethyl acetate 4:1); δ_H (500 MHz, $CDCl_3$): 0.32 (s, 9H, CH_3), 0.39 (s, 9H, CH_3), 5.17 (d, 1H, *J* 13.1 Hz, H7), 5.30 (dd, 1H, *J* 2.1 and 13.1 Hz, H7'), 6.19 (s, 1H, H5), 7.30-7.39 (m, 5H, HAr), 7.48 (s, 1H, HAr); δ_C (126 MHz, $CDCl_3$): 1.5 (CH_3), 1.6 (CH_3), 73.4 (CH_2, C7), 85.3 (CH, C5), 127.0 (CHAr), 128.4 (CHAr), 128.9 (CHAr), 132.4 (CAr), 134.9 (CHAr), 139.4 (CAr), 141.8 (CAr), 159.5 (CAr), 174.0 (CAr); ν_{max}/cm^{-1} (neat) 2955, 2900, 1596, 1578, 1449, 1250; m/z (AP+) 340 ($[M-H]^+$, 40%), 286 (100%); HRMS calc. for $C_{19}H_{27}N_1OSi_2$ 340.1547, found 340.1546 $[M-H]^+$.

***Diethyl 5-phenyl-5,7-dihydrofuro[3,4-b]pyridine-2,3-dicarboxylate* 3.5100**



R_f 0.46 (hexane/ethyl acetate 7:3); δ_H (500 MHz, $CDCl_3$): 1.34 (t, 3H, *J* 7.1 Hz, CH_3), 1.42 (t, 3H, *J* 7.2 Hz, CH_3), 4.31-4.38 (m, 2H, OCH_2), 4.47 (q, 2H, *J* 7.2 Hz, OCH_2), 5.23 (dd, 1H, *J* 1.6 and 14.5 Hz, H7), 5.36 (dd, 1H, *J* 2.3 and 14.5 Hz, H7'), 6.25 (s, 1H, H5), 7.31-7.33 (m, 2H, HAr), 7.36-7.42 (m, 3H, HAr), 7.83 (s, 1H, HAr); δ_C (126 MHz, $CDCl_3$): 14.2 (CH_3), 14.3 (CH_3), 62.4 (OCH_2), 62.7 (OCH_2), 72.8 (CH_2, C7), 84.8 (CH, C5), 125.7 (CAr), 127.0 (CHAr), 129.1 (CHAr), 129.2 (CHAr), 132.3 (CHAr), 137.2 (CAr), 140.4 (CAr), 152.0 (CAr), 163.8 (C), 165.3 (C=O), 166.5 (C=O); ν_{max}/cm^{-1} (neat) 3055, 2985, 2865, 1726 (C=O), 1606, 1571, 1422, 1372, 1265; m/z (AP+) 342 ($[M+H]^+$, 100%); HRMS calc. for $C_{19}H_{20}N_zO_5$ 342.1336, found 342.1338 $[M+H]^+$.

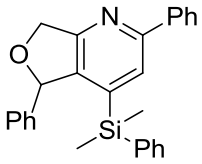
***Tetraethyl 6-((phenyl(2,3,4,5-tetrakis(ethoxycarbonyl)phenyl)methoxy)methyl)pyridine-2,3,4,5-tetracarboxylate* 3.101**



R_f 0.18 (hexane/ethyl acetate 7:3); δ_H (500 MHz, $CDCl_3$): 1.12 (t, 3H, *J* 7.1 Hz, CH_3), 1.16 (t, 3H, *J* 7.2 Hz, CH_3), 1.30-1.39 (m, 18H, CH_3), 3.93-4.04 (m, 2H, OCH_2), 4.09-4.22 (m, 2H, OCH_2), 4.25-4.43 (m, 12H, OCH_2), 4.79 (d, 1H, *J* 12.2 Hz, OC*H*H'), 4.82 (d, 1H, *J* 12.2 Hz, OCH*H*'), 5.85 (s, 1H, CH), 7.22-7.29 (m, 5H, CHAr), 8.26 (s, 1H, CHAr); δ_C (126 MHz, $CDCl_3$):13.8 (CH_3), 13.9 (CH_3), 14.0 (CH_3), 14.0 (CH_3), 14.1 (CH_3), 14.2 (CH_3), 14.2 (CH_3), 14.3 (CH_3), 62.2 (CH_2), 62.3 (CH_2), 62.4 (CH_2), 62.6 (CH_2), 62.6 (CH_2), 62.8 (CH_2), 62.9 (CH_2),

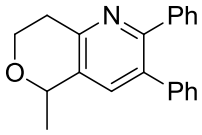
63.0 (CH_2), 71.2 (CH_2), 80.2 (CH), 127.6 (CAr), 128.0 (CHAr), 128.5 (CHAr), 128.7 (CHAr), 129.2 (CAr), 130.7 (CAr), 131.0 (CHAr), 131.3 (CAr), 134.4 (CAr), 135.6 (CAr), 139.1 (CAr), 140.7 (CAr), 141.7 (CAr), 148.1 (CAr), 157.7 (CAr), 164.2 (C=O), 164.5 (C=O), 164.9 (C=O), 165.1 (C=O), 165.2 (C=O), 165.7 (C=O), 166.5 (C=O), 167.0 (C=O); ν_{max}/cm^{-1} (neat) 2984, 2940, 2904, 1726 (C=O), 1567, 1227, 1190, 1094, 1016; m/z (AP+) 852 ($[M+H]^+$, 100%); HRMS calc. for $C_{43}H_{50}NO_{17}$ 852.3073, found 852.3064 $[M+H]^+$.

***4-(Dimethyl(phenyl)silyl)-2,5-diphenyl-5,7-dihydrofuro[3,4-b]pyridine* 3.105**



R_f 0.54 (hexane/ethyl acetate 9:1); δ_H (500 MHz, $CDCl_3$): 0.07 (s, 3H, CH_3), 0.33 (s, 3H, CH_3), 5.11 (d, 1H, *J* 13.4 Hz, H7), 5.25 (dd, 1H, *J* 2.1 and 13.4 Hz, H7'), 5.92 (d, 1H, *J* 2.1 Hz, H5), 6.91 (d, 2H, *J* 7.0 Hz, HAr), 7.23-7.36 (m, 7H, HAr), 7.40-7.51 (m, 4H, CHAr), 7.74 (s, 1H, HAr), 7.97 (d, 2H, *J* 7.3 Hz, HAr); δ_C (126 MHz, $CDCl_3$): -3.0 (CH_3), -1.9 (CH_3), 72.0 (CH_2, C7), 85.9 (CH, C5), 126.2 (CHAr, C3), 127.3 (CHAr), 128.3 (CHAr), 128.8 (CHAr), 129.0 (CHAr), 129.0 (CHAr), 129.0 (CHAr), 129.2 (CHAr), 129.9 (CHAr), 134.4 (CHAr), 136.0 (CAr), 138.1 (CAr), 139.6 (CAr), 141.1 (CAr), 144.2 (CAr), 156.9 (CAr), 160.5 (CAr); ν_{max}/cm^{-1} (neat) 2953, 2998, 1592, 1574, 1450, 1248; m/z (ES+) 408 $[M+H]^+$, 100%. The sample decomposed before HRMS could be obtained.

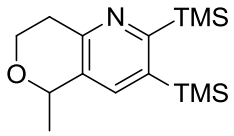
***5-Methyl-2,3-diphenyl-7,8-dihydro-5H-pyrano[4,3-b]pyridine* 3.107g**



R_f 0.34 (hexane/ethyl acetate 4:2); δ_H (500 MHz, $CDCl_3$): 1.60 (d, 3H, *J* 6.5 Hz, CH_3), 3.00 (td, 1H, *J* 17.1 and 3.0 Hz, H8), 3.24-3.32 (m, 1H, H8'), 3.97 (ddd, 1H, *J* 3.8, 10.5 and 11.5 Hz, H7), 4.33 (ddd, 1H, *J* 3.0, 5.9 and 11.5 Hz, H7'), 4.93 (q, 1H, *J* 6.5 Hz, H5), 7.13-7.17 (m, 2H, HAr), 7.21-7.28 (m, 6H, HAr),

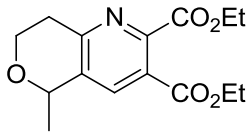
7.31-7.35 (m, 2H, HAr), 7.42 (s, 1H, H4); δ_C (126 MHz, $CDCl_3$): 21.6 (CH_3), 32.4 (CH_2, C8), 64.4 (CH_2, C7), 72.0 (CH, C5), 127.3 (CHAr), 127.9 (CHAr), 128.2 (CHAr), 128.5 (CHAr), 129.8 (CHAr), 130.1 (CHAr) 133.7 (CAr), 134.3 (CAr), 135.2 (CHAr, C4), 140.1 (CAr), 140.1 (CAr), 152.7 (CAr), 155.4 (CAr); ν_{max}/cm^{-1} (neat) 3056, 2974, 2932, 2852, 1545, 1449, 1428, 1372, 1113; m/z (AP+) 302 ($[M+H]^+$, 100%); HRMS calc. for $C_{21}H_{20}NO$ 302.1540, found 302.1539 $[M+H]^+$.

***5-Methyl-2,3-bis(trimethylsilyl)-7,8-dihydro-5H-pyrano[4,3-b]pyridine* 3.107h**



R_f 0.52 (hexane/ethyl acetate 9:1); δ_H (500 MHz, $CDCl_3$): 0.35 (s, 9H, CH_3), 0.36 (s, 9H, CH_3), 1.51 (d, 3H, *J* 6.5 Hz, CH_3), 2.84 (dt, 1H, *J* 17.0 and 2.9 Hz, H8), 3.10-3.18 (m, 1H, H8'), 3.88 (ddd, 1H, *J* 3.8, 10.9 and 11.5 Hz, H7), 4.24 (ddd, 1H, *J* 2.9, 5.9 and 11.5 Hz, H7'), 4.81 (q, 1H, *J* 6.5 Hz, H5), 7.48 (s, 1H, H4); δ_C (126 MHz, $CDCl_3$): 1.3 (CH_3), 1.5 (CH_3), 21.4 (CH_3), 32.6 (CH_2, C8), 64.6 (CH_2, C7), 72.0 (CH, C5), 132.2 (CAr) 137.1 (CHAr, C4), 138.3 (CAr), 152.4 (CAr), 171.5 (CAr); ν_{max}/cm^{-1} (neat) 3051, 2960, 1535, 1420, 1373, 1264; m/z (ES+) 326 (100%), 294 ($[M+H]^+$, 25%), 292 $[M-H]^+$, 70%. The sample decomposed before HRMS could be obtained.

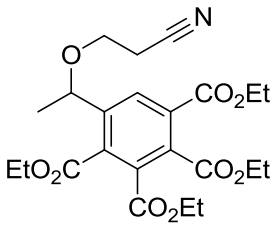
***Diethyl 5-methyl-7,8-dihydro-5H-pyrano[4,3-b]pyridine-2,3-dicarboxylate* 3.107a**



R_f 0.45 (hexane/ethyl acetate 7:3); δ_H (500 MHz, $CDCl_3$): 1.37 (t, 3H, *J* 7.2 Hz, CH_3), 1.40 (t, 3H, *J* 7.2 Hz, CH_3), 1.57 (d, 3H, *J* 6.6 Hz, CH_3), 2.94-2.99 (m, 1H, H8), 3.19-3.26 (m, 1H, H8'), 3.88 (td, 1H, *J* 3.8, 11.5, H7), 4.27 (ddd, 1H, *J* 2.9, 6.0 and 11.5 Hz, H7'), 4.37 (q, 1H, *J* 7.2 Hz, OCH_2), 4.45 (q, 1H, *J* 7.2 Hz, OCH_2), 4.86 (q, 1H, *J* 6.6 Hz, H5), 7.92 (s, 1H, H4); δ_C (126 MHz, $CDCl_3$): 14.2 (CH_3), 14.3 (CH_3), 21.3 (CH_3), 32.6 (CH_2, C8), 62.1 (OCH_2), 62.4 (OCH_2), 63.6

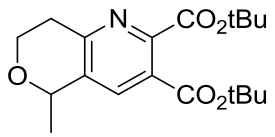
(CH_2, C7), 71.8 (CH, C5), 134.0 (CHAr, C4), 134.4 (CAr), 136.6 (CAr), 149.9 (CAr), 157.6 (CAr), 165.2 (C=O), 166.8 (C=O); ν_{max}/cm^{-1} (neat) 2999, 2978, 2867, 1741 (C=O), 1607, 1565, 1427, 1370, 1261; m/z (AP+) 294 $[M+H]^+$, 100%; HRMS calc. for $C_{15}H_{20}NO_5$ 294.1336, found 294.1338 $[M+H]^+$.

***Tetraethyl 5-(1-(2-cyanoethoxy)ethyl)benzene-1,2,3,4-tetracarboxylate* 3.109a**



R_f 0.22 (hexane/ethyl acetate 7:3); δ_H (500 MHz, $CDCl_3$): 1.30-1.37 (m, 12H, CH_3), 1.47 (d, 1H, *J* 6.4 Hz, CH_3), 2.55 (t, 2H, *J* 6.2 Hz, $CH_2C{\equiv}N$), 3.42-3.50 (m, 2H, OCHH'), 4.28 (q, 2H, *J* 7.2 Hz, OCH_2), 4.27-4.37 (m, 6H, OCH_2), 4.66 (q, 1H, *J* 6.4 Hz, CH), 8.18 (s, 1H, HAr); δ_C (126 MHz, $CDCl_3$): 14.0 (CH_3), 14.2 (CH_3), 14.3 (CH_3), 19.1 (CH_2, CH_2CN), 23.4 (CH_3), 62.3 (OCH_2), 62.4 (OCH_2), 62.5 (OCH_2), 62.7 (OCH_2), 63.9 (CH_2), 75.4 (CH), 117.8 (C, C≡N), 130.4 (CHAr), 130.5 (CAr), 131.7 (CAr), 134.7 (CAr), 135.5 (CAr), 143.3 (CAr), 164.8 (C=O), 165.5 (C=O), 166.8 (C=O), 167.0 (C=O); ν_{max}/cm^{-1} (neat) 2983, 2939, 2904, 2252, 1725 (C=O), 1235, 1194, 1178, 1156, 1099, 1019; m/z (AP+) 464 ($[M+H]^+$, 100%); HRMS calc. for $C_{23}H_{33}N_2O_9$ 481.2191, found 481.2185 $[M+NH_4]^+$.

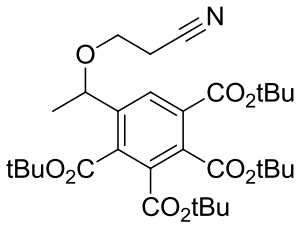
***Di-tert-butyl 5-methyl-7,8-dihydro-5H-pyrano[4,3-b]pyridine-2,3-dicarboxylate* 3.107i**



R_f 0.49 (hexane/ethyl acetate 7:3); δ_H (500 MHz, $CDCl_3$): 1.57 (d, 3H, *J* 6.6 Hz, CH_3), 1.58 (s, 6H, CH_3), 1.60 (s, 6H, CH_3), 1.62 (s, 6H, CH_3), 2.91-2.96 (m, 1H, H8), 3.16-3.24 (m, 1H, H8'), 3.82-3.89 (m, 1H, H7), 4.23-4.29 (m, 1H, H7'), 4.82-4.86 (m, 1H, H5), 7.74 (s, 1H, H4); δ_C (126 MHz, $CDCl_3$): 21.4 (CH_3), 28.2

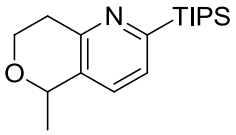
(CH_3), 28.3 (CH_3), 28.4 (CH_3), 32.6 (CH_2, C8), 63.8 (CH_2, C7), 71.8 (CH, C5), 82.7 (C), 83.1 (C), 133.6 (CAr), 133.9 (CHAr, C4), 135.8 (CAr), 150.8 (CAr), 156.8 (CAr), 164.5 (C=O), 166.1 (C=O); ν_{max}/cm^{-1} (neat) 2979, 2935, 1718 (C=O), 1368, 1302, 1278, 1245, 1170, 1118, 1094; m/z (AP+) 348 ($[M-H]^+$, 40%), 270 100%; 238 ($[M-(2^tBu)+H]^+$, 80%); HRMS calc. for $C_{19}H_{28}NO_5$ 350.1962, found 350.1964 $[M+H]^+$.

***Tetra-tert-butyl 5-(1-(2-cyanoethoxy)ethyl)benzene-1,2,3,4-tetracarboxylate* 3.109i**



R_f 0.57 (hexane/ethyl acetate 7:3); δ_H (500 MHz, $CDCl_3$): 1.48 (d, 1H, *J* 6.4 Hz, CH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.57 (s, 9H, $C(CH_3)_3$), 1.58 (s, 9H, $C(CH_3)_3$), 1.59 (s, 9H, $C(CH_3)_3$), 2.49-2.59 (m, 2H, CH_2CN), 3.41-3.48 (m, 2H, OCHH), 4.71 (q, 1H, *J* 6.4 Hz, CH), 7.84 (s, 1H, HAr); δ_C (126 MHz, $CDCl_3$): 19.2 (CH_2, CH_2CN), 24.1 (CH_3), 28.2 (CH_3), 28.2 (CH_3), 28.3 (CH_3), 28.4 (CH_3), 63.8 (CH_2), 75.6 (CH), 82.8 (C), 83.3 (C), 84.0 (C), 84.1 (C), 117.8 (C, C≡N), 127.8 (CHAr), 133.5 (CAr), 133.7 (CAr), 134.0 (CAr), 134.6 (CAr), 142.0 (CAr), 164.7 (C=O), 165.8 (C=O), 166.0 (C=O), 166.1 (C=O); ν_{max}/cm^{-1} (neat) 2981, 2935, 2253, 1718 (C=O), 1368, 1251, 1184, 1107; m/z (AP+) 576 ($[M+H]^+$, 5%), 354 (50%), 294 (100%); HRMS calc. for $C_{31}H_{49}N_2O_9$ 593.3433, found 593.3439 $[M+NH_4]^+$.

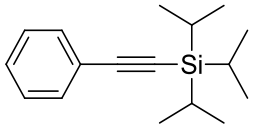
***5-Methyl-2-(triisopropylsilyl)-7,8-dihydro-5H-pyrano[4,3-b]pyridine* 3.107k**



R_f 0.54 (hexane/ethyl acetate 9:1); δ_H (400 MHz, $CDCl_3$): 1.09 (d, 9H, CH_3), 1.11 (d 9H, CH_3) 1.41-1.48 (m, 3H, CH), 1.52 (d, 3H, *J* 6.5 Hz, CH_3), 2.88 (td,

1H, *J* 16.8 and 3.2 Hz, H8), 3.17 (ddd, 1H, *J* 6.0, 10.4 and 16.8 Hz, H8'), 3.90 (ddd, 1H, *J* 3.9, 10.5 and 11.5 Hz, H7), 4.25 (ddd, 1H, *J* 2.9, 6.0 and 11.5 Hz, H7'), 4.82 (q, 1H, *J* 6.5 Hz, H5), 7.22 (d, 1H, *J* 7.8 Hz, HAr), 7.75 (d, 1H, *J* 7.8 Hz, HAr); δ_C (100 MHz, $CDCl_3$): 11.2 (CH), 18.9 (CH_3), 21.4 (CH_3), 33.0 (CH_2, C8), 64.5 (CH_2, C7), 72.1 (CH, C5), 128.5 (CHAr), 129.5 (CHAr), 133.3 (CAr), 153.6 (CAr), 162.9 (CAr); ν_{max}/cm^{-1} (neat) 3059, 2944, 2896, 2865, 1463, 1373, 1264; m/z (AP+) 306 ($[M+H]^+$, 100%). The sample decomposed before HRMS could be obtained.

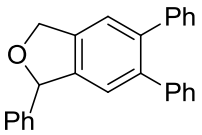
Tri-isopropyl(phenylethynyl)silane



Ethyl magnesium chloride (8.3 mL of a 2 M solution in THF, 16.6 mmol) was added dropwise to a stirred solution of phenyl acetylene (1.7 mL, 1.6 g, 15.48 mmol) in THF (17.0 mL) at -78 ºC under nitrogen. After 1 h, TIPSCl (2.3 mL, 2.1 g, 11.1 mmol) was added very slowly. The reaction mixture was allowed to warm to rt temperature and then heated under reflux overnight. The reaction was quenched with an aq. sat. solution of NH_4Cl (20 mL), extracted with ethyl acetate (3 × 20 mL), and the combined organic layers dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (hexane) to yield (2.1 g, 75%) as a colourless liquid.

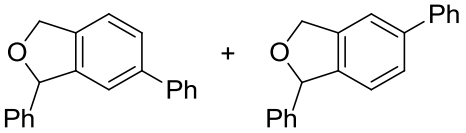
R_f 0.78 (hexane), δ_H (500 MHz, $CDCl_3$): 1.19 (brs, 18H, CH_3), 1.21 (brs, 3H, CH_3), 7.33-7.34 (m, 3H, HAr), 7.52-7.54 (m, 2H, HAr). δ_C (126 MHz, $CDCl_3$): 11.6 (CH), 18.9 (CH_3), 90.6 (C, C≡C), 107.4 (C, C≡C), 123.8 (CAr), 128.4 (CHAr), 128.5 (CHAr), 132.3 (CHAr); ν_{max}/cm^{-1} (neat) 2942, 2864, 2156, 1488, 1462, 1218; m/z (AP+) 517 ($[dimer]^+$, 100%), 259 ($[M+H]^+$, 15%), 217 ($[M-CH(CH_3)_2]^+$, 70%); HRMS calc. for $C_{17}H_{30}NSi$ 276.2142, found 276.2145 $[M+NH_4]^+$.

***1,5,6-Triphenyl-1,3-dihydroisobenzofuran* 3.110g**



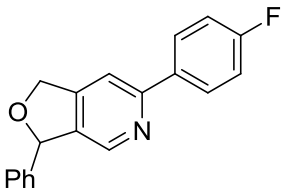
R_f 0.57 (hexane/ethyl acetate 4:1); δ_H (500 MHz, $CDCl_3$): 5.32 (d, 1H, *J* 12.3 Hz, H3), 5.46 (dd, 1H, *J* 2.1 and 12.3 Hz, H3'), 6.27 (brs, 1H, H1), 7.07-7.09 (m, 2H, HAr), 7.11 (s, 1H, HAr), 7.15-7.18 (m, 5H, HAr), 7.20-7.23 (m, 3H, HAr), 7.32-7.34 (m, 1H, HAr), 7.36-7.41 (m, 3H, HAr), 7.43-7.45 (m, 2H, HAr); δ_C (126 MHz, $CDCl_3$): 73.4 (CH_2, C3), 86.4 (CH, C1), 123.2 (CHAr), 124.5 (CHAr), 126.8 (CHAr), 126.8 (CHAr), 127.2 (CHAr), 128.1 (CHAr), 128.2 (CHAr), 128.4 (CHAr), 128.9 (CHAr), 130.1(CHAr), 138.8 (CAr), 140.6 (CAr), 140.7 (CAr), 141.6 (CAr), 141.6 (CAr), 141.8 (CAr), 142.2 (CAr); ν_{max}/cm^{-1} (neat) 3063, 3026, 2921, 2850, 1601, 1493, 1473, 1447, 1402, 1349, 1265; m/z (AP+) 349 ($[M+H]^+$, 100%); HRMS calc. for $C_{26}H_{21}O$ 349.1587, found 3349.1585 $[M+H]^+$.

***1,5- and 1,6-Diphenyl-1,3-dihydroisobenzofuran* 3.110k**



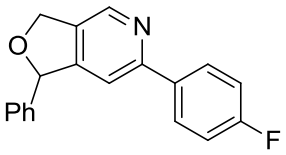
R_f 0.28 (hexane/ethyl acetate 9:1); δ_H (500 MHz, $CDCl_3$): 5.26 (d, 1H, *J* 12.1 Hz, CH), 5.28 (d, 1H, *J* 11.3 Hz, CH), 5.40 (dd, 1H, *J* 2.3 and 12.2 Hz, CH), 5.41 (dd, 1H, *J* 2.1 and 12.1 Hz, CH), 6.22 (brs, 2H, CH), 7.11 (d, 1H, *J* 7.9 Hz, HAr), 7.24 (s, 1H, HAr), 7.31-7.47 (m, 18H, HAr), 7.51-7.54 (m, 4H, HAr), 7.57-7.59 (m, 2H, HAr); δ_C (126 MHz, $CDCl_3$): 73.4 (CH_2), 73.5 (CH_2), 86.3 (CH), 86.5 (CH), 119.9 (CHAr), 121.3 (CHAr), 121.5 (CHAr), 122.8 (CHAr), 127.1 (CHAr), 127.2 (CHAr), 127.2 (CHAr), 127.3 (CHAr), 127.4 (CHAr), 127.5 (CHAr), 127.6 (CHAr), 127.6 (CHAr), 128.4 (CHAr), 128.4 (CHAr), 128.8 (CHAr), 129.0 (CHAr), 129.0 (CHAr), 138.5 (CAr), 140.2 (CAr), 141.1 (CAr), 141.2 (CAr), 141.2 (CAr), 141.4 (CAr), 142.2 (CAr), 142.3 (CAr), 143.1 (CAr); ν_{max}/cm^{-1} (neat) 3021, 2857, 2870, 1613, 1484, 1456, 1320, 1271; m/z (ES+) 271 ($[M-H]^+$,100%); HRMS calc. for $C_{20}H_{20}NO$ 273.1539, found 273.1536 $[M+H]^+$.

***6-(4-Fluorophenyl)-3-phenyl-1,3-dihydrofuro[3,4-c]pyridine* 3.111a**



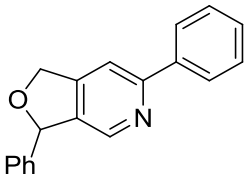
R_f 0.33 (hexane/ethyl acetate 4:1); δ_H (400 MHz, $CDCl_3$): 5.23 (d, 1H, *J* 13.5 Hz, H1), 5.36 (dd, 1H, *J* 2.2 and 13.5 Hz, H1'), 6.27 (brs, 1H, H3), 7.15 (t, 2H, *J* 8.7 Hz, HAr), 7.33-7.41 (m, 5H, HAr), 7.62 (s, 1H, H7), 7.94-7.97 (m, 2H, HAr), 8.39 (s, 1H, H4); δ_C (100 MHz, $CDCl_3$): 72.8 (CH_2, C1), 84.7 (CH, C3), 113.1 (CHAr, C7), 116.0 (d, *J* 21.7 Hz, CHAr), 127.0 (CHAr), 128.8 (CHAr), 129.0 (CHAr), 129.1 (d, *J* 8.5 Hz, CHAr), 135.5 (d, *J* 3.1 Hz, CAr), 141.1 (CAr), 144.1 (CHAr, C4), 150.3 (CAr), 156.1 (CAr), 162.8 (CAr), 164.8 (CAr); ν_{max}/cm^{-1} (neat) 3035, 2863, 1600, 1511, 1477, 1456, 1417, 1383, 1212, 1154; m/z (AP+) 292 ($[M+H]^+$, 100%); HRMS calc. for $C_{19}H_{15}NOF$ 292.1132, found 292.1131 $[M+H]^+$.

***6-(4-Fluorophenyl)-1-phenyl-1,3-dihydrofuro[3,4-c]pyridine* 3.112a**



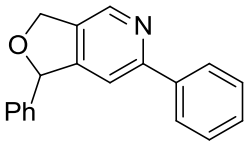
R_f 0.21 (hexane/ethyl acetate 4:1); δ_H (500 MHz, $CDCl_3$): 5.29 (d, 1H, *J* 12.5 Hz, H3), 5.43 (d, 1H, *J* 12.5 Hz, H3'), 6.18 (s, 1H, H1), 7.09-7.13 (m, 2H, HAr), 7.35-7.41 (m, 6H, HAr, H7), 7.88-7.92 (m, 2H, HAr), 8.65 (s, 1H, H4); δ_C (126 MHz, $CDCl_3$): 71.7 (CH_2, C3), 86.0 (CH, C1), 114.2 (CHAr, C7), 115.9 (d, *J* 21.7 Hz, CHAr), 127.2 (CHAr), 128.9 (CHAr), 129.0 (CHAr), 129.1 (CHAr), 135.5 (d, *J* 3.1 Hz, CAr), 140.7 (CAr), 142.9 (CHAr, C4), 152.8 (CAr), 156.2 (CAr), 162.7 (CAr), 164.7 (CAr); ν_{max}/cm^{-1} (neat) 3063, 3027, 2856, 1599, 1512, 1475, 1224, 1156; m/z (AP+) 292 ($[M+H]^+$, 100%); HRMS calc. for $C_{19}H_{15}NOF$ 292.1132, found 292.1132 $[M+H]^+$.

***3,6-Diphenyl-1,3-dihydrofuro[3,4-c]pyridine* 3.111b**



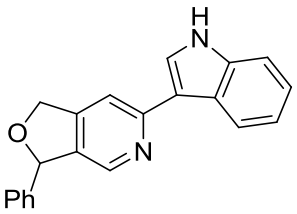
R_f 0.30 (hexane/ethyl acetate 4:1); δ_H (500 MHz, $CDCl_3$): 5.24 (d, 1H, *J* 13.5 Hz, H1), 5.37 (dd, 1H, *J* 2.1 and 13.5 Hz, H1'), 6.28 (brs, 1H, H3), 7.33-7.44 (m, 6H, HAr), 7.48 (t, 2H, *J* 7.4 Hz, HAr),7.67 (s, 1H, H7), 7.98 (d, 2H, *J* 7.4 Hz, HAr), 8.42 (s, 1H, H4); δ_C (126 MHz, $CDCl_3$): 72.8 (CH_2, C1), 84.8 (CH, C3), 113.4 (CHAr, C7), 127.1 (CHAr), 127.3 (CHAr), 128.8 (CHAr), 129.0 (CHAr), 129.3 (CHAr), 136.9 (CAr), 139.3 (CAr), 141.2 (CAr), 144.1 (CHAr, C4), 150.2 (CAr), 157.1 (CAr); ν_{max}/cm^{-1} (neat) 3061, 2919, 2853, 1605, 1565, 1474, 1449, 1385, 1042, 1024; m/z (AP+) 274 ($[M+H]^+$, 100%); HRMS calc. for $C_{19}H_{16}NO$ 2274.1226, found 274.1229 $[M+H]^+$.

***1,6-Diphenyl-1,3-dihydrofuro[3,4-c]pyridine* 3.112b**



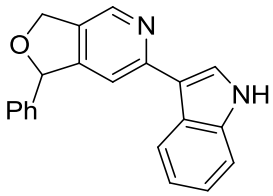
R_f 0.17 (hexane/ethyl acetate 4:1); δ_H (500 MHz, $CDCl_3$): 5.29 (d, 1H, *J* 12.5 Hz, H3), 5.43 (dd, 1H, *J* 2.2 and 12.5 Hz, H3'), 6.19 (brs, 1H, H1), 7.33-7.45 (m, 9H, Har, H7), 7.92 (d, 2H, *J* 7.1 Hz, HAr), 8.68 (s, 1H, H4); δ_C (126 MHz, $CDCl_3$): 71.7 (CH_2, C3), 86.0 (CH, C1), 114.5 (CHAr, C7), 127.2 (CHAr), 127.3 (CHAr), 128.8 (CHAr), 129.0 (CHAr), 129.1 (CHAr), 129.2 (CHAr), 134.0 (CAr), 139.4 (CAr), 140.7 (CAr), 143.0 (CHAr, C4), 152.7 (CAr), 157.3 (CAr); ν_{max}/cm^{-1} (neat) 3028, 2919, 2848, 1612, 1563, 1474, 1454, 1336, 1017; m/z (AP+) 274 ($[M+H]^+$, 100%); HRMS calc. for $C_{19}H_{16}NO$ 2274.1226, found 274.1229 $[M+H]^+$.

***6-(1H-Indol-3-yl)-3-phenyl-1,3-dihydrofuro[3,4-c]pyridine* 3.111d**



R_f 0.43 (hexane/ethyl acetate 1:1); δ_H (500 MHz, CD_3COCD_3): 5.19 (d, 1H, *J* 13.4 Hz, H1), 5.36 (dd, 1H, *J* 1.8 and 13.4 Hz, H1'), 6.26 (brs, 1H, H3), 7.13-7.20 (m, 2H, HAr), 7.31-7.34 (m, 1H, HAr), 7.39 (t, 2H, *J* 7.5 Hz, HAr), 7.44-7.49 (m, 3H, HAr), 7.84 (s, 1H, H7), 8.05 (d, 1H, *J* 2.3 Hz, HAr), 8.36 (s, 1H, H4), 8.95 (d, 1H, *J* 8.0 Hz, HAr), 10.64 (brs, 1H, NH); δ_C (126 MHz, CD_3COCD_3): 72.4 (CH_2, C1), 84.3 (CH, C3), 111.8 (CHAr), 112.1 (CHAr, C7), 116.7 (CAr), 120.3 (CHAr), 122.0 (CHAr), 122.1 (CHAr), 125.6 (CHAr), 126.0 (CAr), 126.7 (CHAr), 128.1 (CHAr), 128.7 (CHAr), 134.9 (CAr), 137.7 (CAr), 142.8 (CAr), 143.4 (CHAr, C4), 149.5 (CAr), 155.0 (CAr); ν_{max}/cm^{-1} (neat) 3170, 2964, 2921, 2851, 1613, 1547, 1449, 1242, 1020; m/z (AP+) 313 ($[M+H]^+$, 100%); HRMS calc. for $C_{21}H_{17}N_2O$ 313.1346, found 313.1340 $[M+H]^+$.

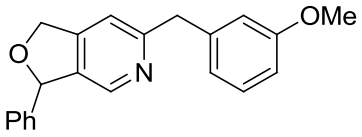
***6-(1H-Indol-3-yl)-1-phenyl-1,3-dihydrofuro[3,4-c]pyridine* 3.112d**



R_f 0.23 (hexane/ethyl acetate 1:1); δ_H (500 MHz, CD_3COCD_3): 5.22 (d, 1H, *J* 12.2 Hz, H3), 5.40 (dd, 1H, *J* 1.9 and 12.2 Hz, H3'), 6.19 (brs, 1H, H1), 7.12-7.18 (m, 2H, HAr), 7.30-7.33 (m, 1H, HAr), 7.38 (t, 2H, *J* 7.6 Hz, HAr), 7.45 (d, 3H, *J* 7.5 Hz, HAr), 7.54 (s, 1H, H7), 7.96 (d, 1H, *J* 1.9 Hz, HAr), 8.50 (d, 1H, *J* 7.8 Hz, HAr), 8.66 (s, 1H, H4), 10.59 (brs, 1H, NH); δ_C (126 MHz, CD_3COCD_3): 71.4 (CH_2, C3), 85.4 (CH, C1), 111.8 (CHAr), 112.9 (CHAr, C7), 116.6 (CAr), 120.3 (CHAr), 122.1 (CHAr), 122.2 (CHAr), 125.4 (CHAr), 126.0 (CAr), 126.9 (CHAr), 128.2 (CHAr), 128.8 (CHAr), 131.5 (CAr), 137.6 (CAr), 142.2 (CAr), 142.6 (CHAr, C4), 152.2 (CAr), 155.1 (CAr); ν_{max}/cm^{-1} (neat) 3305, 3132, 3062,

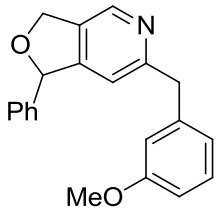
2925, 2856, 1613, 1543, 1448, 1266, 124, 1004; m/z (AP+) 313 ($[M+H]^+$, 100%); HRMS calc. for $C_{21}H_{17}N_2O$ 313.1335, found 313.1340 $[M+H]^+$.

6-(3-Methoxyphenyl)-3-phenyl-1,3-dihydrofuro[3,4-c]pyridine **3.111e**



R_f 0.32 (hexane/ethyl acetate 4:1); δ_H (500 MHz, $CDCl_3$): 3.78 (s, 3H, CH_3), 4.17 (s, 2H, CH_2Ar), 5.10 (d, 1H, *J* 13.7 Hz, H1), 5.23 (dd, 1H, *J* 1.9 and 13.7 Hz, H1'), 6.20 (brs, 1H, H3), 6.78-6.84 (m, 3H, HAr), 7.06 (s, 1H, H7),7.24 (t, 1H, *J* 7.9 Hz, HAr), 7.23-7.34 (m, 5H, HAr), 8.28 (s, 1H, H4); δ_C (126 MHz, $CDCl_3$): 44.7 (CH_2, CH_2Ar), 55.4 (CH_3), 72.6 (CH_2, C1), 84.7 (CH, C3), 112.1 (CHAr), 115.2 (CHAr), 115.9 (CHAr, C7), 121.8 (CHAr), 127.0 (CHAr), 128.7 (CHAr), 129.0 (CHAr), 130.0 (CHAr), 136.1 (CAr), 141.0 (CAr), 141.3 (CAr), 143.6 (CHAr, C4), 150.0 (CAr), 160.0 (CAr), 160.2 (CAr); ν_{max}/cm^{-1} (neat) 3055, 2937, 2837, 1599, 1584, 1489, 1454, 1393, 1260, 1041; m/z (AP+) 318 ($[M+H]^+$, 70%); HRMS calc. for $C_{21}H_{20}NO_2$ 318.1500, found 318.1492 $[M+H]^+$.

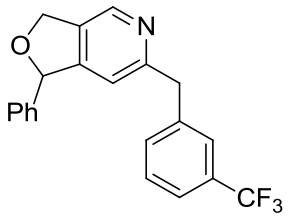
6-(3-Methoxybenzyl)-1-phenyl-1,3-dihydrofuro[3,4-c]pyridine **3.112e**



R_f 0.16 (hexane/ethyl acetate 4:1); δ_H (500 MHz, $CDCl_3$): 3.74 (s, 3H, CH_3), 4.06 (d, 1H, 14.7 Hz, C*H*H'Ph), 4.14 (d, 1H, 14.7 Hz, CH*H*'Ph), 5.20 (d, 1H, *J* 12.3 Hz, H3), 5.35 (dd, 1H, *J* 2.4 and 12.3 Hz, H3'), 6.08 (brs, 1H, H1), 6.73-6.81 (m, 3H, HAr), 6.89 (s, 1H, H7), 7.19 (t, 1H, J 7.3 Hz, HAr), 7.26-7.39 (m, 5H, HAr), 8.53 (s, 1H, H4); δ_C (126 MHz, $CDCl_3$): 44.7 (CH_2, CH_2Ph), 55.4 (CH_3), 71.6 (CH_2, C3), 85.8 (CH, C1), 112.1 (CHAr), 114.8 (CHAr), 117.1 (CHAr, C7), 121.6 (CHAr), 127.1 (CHAr), 128.7 (CHAr), 129.0 (CHAr), 129.8 (CHAr), 133.2 (CAr), 140.8 (CAr), 141.2 (CAr), 142.6 (CHAr, C4), 152.4 (CAr), 160.0 (CAr), 160.1 (CAr); ν_{max}/cm^{-1} (neat) 3053, 2924, 2837, 1598, 1488, 1263, 1149, 1040; m/z

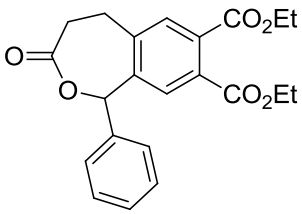
(AP+) 318 ([M+H]$^+$, 100%); HRMS calc. for $C_{21}H_{20}NO_2$ 318.1489, found 318.1491 [M+H]$^+$.

***1-Phenyl-6-(3-(trifluoromethyl)benzyl)-1,3-dihydrofuro[3,4-c]pyridine* 3.112f**



R_f 0.26 (hexane/ethyl acetate 4:1); δ_H (500 MHz, $CDCl_3$): 4.33 (s, 2H, CH_2Ar), 5.22 (d, 2H, *J* 12.3 Hz, H3), 5.35 (dd, 1H, *J* 2.3 and 12.3 Hz, H3'), 6.09 (brs, 1H, H1), 6.82 (s, 1H, H7), 7.25-7.37 (m, 7H, HAr), 7.43 (t, 1H, *J* 7.5 Hz, HAr), 7.64 (d, 1H, *J* 7.7 Hz, HAr), 8.54 (s, 1H, H4); δ_C (126 MHz $CDCl_3$): 40.6 (CH_2, CH_2Ar), 71.6 (CH_2, C3), 85.7 (CH, C1), 117.4 (CHAr, C7), 123.6 (C), 125.8 (CAr), 126.2 (q, *J* 5.8 Hz, CHAr), 126.8 (CHAr), 127.0 (CHAr), 128.8 (CHAr), 129.0 (CHAr), 132.1 (d, *J* 4.1 Hz, CHAr), 133.5 (CAr), 137.8 (CAr), 140.6 (CAr), 142.6 (CHAr, C4), 152.5 (CAr), 159.0 (CAr); ν_{max}/cm^{-1} (neat) 3054, 2988, 2861, 1609, 1483, 1455, 1396, 1313, 1264, 1120; m/z (AP+) 372 (90%), 370 (100%), 356 ([M+H]$^+$, 80%); HRMS calc. for $C_{21}H_{17}NOF_3$ 356.1257, found 356.1253 [M+H]$^+$.

***Diethyl 3-oxo-1-phenyl-1,3,4,5-tetrahydrobenzo[c]oxepine-7,8-dicarboxylate* 3.121**



R_f 0.48 (ethyl acetate); δ_H (500 MHz, $CDCl_3$): 1.29 (t, 3H, *J* 7.1 Hz, CH_3), 1.37 (t, 3H, *J* 7.1 Hz, CH_3), 2.81-2.87 (m, 1H, H5) 3.07-3.12 (m, 1H, H5'), 3.15-3.21 (m, 1H, H4), 3.33-3.34 (m, 1H, H4'), 4.28 (q, 2H, *J* 7.1 Hz, OCH_2), 4.37 (q, 2H, *J* 7.1 Hz, OCH_2), 6.65 (s, 1H, H1), 7.24 (s, 1H, HAr), 7.30 (d, 2H, *J* 7.3 Hz, HAr),

7.39-7.44 (m, 3H, HAr), 7.58 (s, 1H, HAr); δ_C (126 MHz, $CDCl_3$): 14.2 (CH_3), 14.3 (CH_3), 28.6 (CH_2, C5), 33.2 (CH_2, C4), 62.0 (OCH_2), 62.1 (OCH_2), 80.4 (CH, C1), 127.4 (CHAr), 129.1 (CHAr), 129.2 (CHAr), 130.1 (CAr), 130.5 (CHAr), 130.9 (CHAr), 133.3 (CAr), 138.0 (CAr), 139.2 (CAr), 141.4 (CAr), 166.7 (C=O), 167.4 (C=O), 172.5 (C=O); ν_{max}/cm^{-1} (neat) 3059, 2984, 1718 (C=O), 1449, 1368, 1265; m/z (AP+) 383 ($[M+H]^+$, 100%); HRMS calc. for $C_{22}H_{23}O_6$ 383.1500, found 383.1490 $[M+H]^+$.

6.4 Experimental procedure for chapter 4

Following the procedure of Mosmann:[209] 1×10^4 cells/ml were inoculated into each well of a 96-well plate and incubated overnight at 37 °C in a humidified atmosphere containing 5% CO_2. All the compounds were dissolved in DMSO and then diluted in complete cell culture medium to give final test concentrations of 5 and 50 µM and making sure that the maximum final DMSO concentration was not greater than 0.1%. Medium was removed from each well and replaced with compound or control solutions, and the plates then incubated for a further 96 h. After 96 h culture medium was removed and 200 µL of 0.5 $mg.ml^{-1}$ MTT solution in complete medium added to each well. Following a further 4 h incubation, the solution was removed from each well and 150 µL of DMSO added to solubilise the formazan crystals resulting from MTT conversion. Absorbance values for the resulting solutions were read at 550 nm on a microplate reader and cell survival calculated from the ratio of absorbance of treated cells to control cells. Results were expressed in terms of IC50 values (concentration of compound required to kill 50% of cells) and all experiments were performed in triplicate.

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